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Overview of GMP Inspections conducted by Irish Medicines Board

Lorraine Nolan
Acting Inspection Manager
Irish Medicines Board

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Agenda

- Overview of IMB's inspection programme
- Inspection Process
- Particular areas of inspection focus
- Common GMP Deficiencies

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Overview of GMP Inspection Programme (1)

- 84 authorised manufacturers of medicinal products for human use
- 28 authorised manufacturers of veterinary medicinal products (15 H & V)
- 43 authorised manufacturers of investigational medicinal products
- 7 GMP inspectors and others cross-training

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Overview of GMP Inspection Programme (2)

- Routine Inspection every two years as per EU Guideline
- See also under 'Risk Management' below
- Inspections in non – EEA/ non – MRA countries at request of EMEA for centrally authorised products
- Also non – EEA / non – MRA for some nationally authorised products

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Overview of GMP Inspection Programme (3)

- Quality Risk Management
  - Early change to two year inspection frequency unlikely
  - QRM applied to deciding on re - inspection at shorter interval where significant non – compliances identified
  - Quality of manufacturer's approach to QRM will be closely examined

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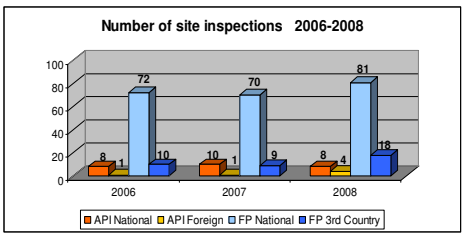
Overview of GMP Inspection Programme (4)



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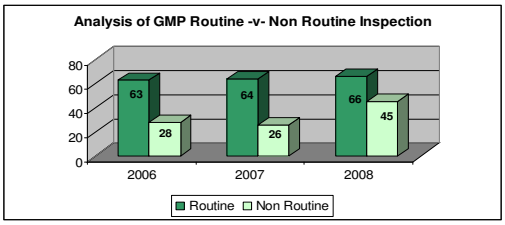
Overview of GMP Inspection Programme (5)



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Overview of API Inspection Programme (1)

- No requirement for Active Substance manufacturers to be authorised
- However, all inspected regularly in relation to requests for GMP certification
- API inspections non-EEA/non-MRA countries at request of EDQM / EMEA

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Overview of API Inspection Programme (2)

- Commenced in the mid 1990s
- Limited number of API sites and IMB Inspectors
- Now, a rolling program of API inspections is in place at 2 to 3 year frequency for 'routine'
- Provision to conduct non-routine inspections:
  - Significant change to premises
  - Introduction of new API, technology, equipment

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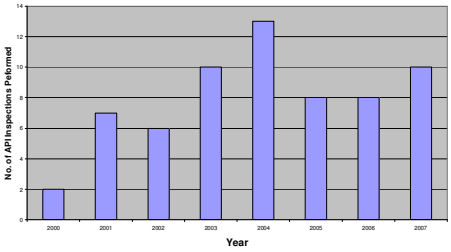
Overview of API Inspection Programme (3)



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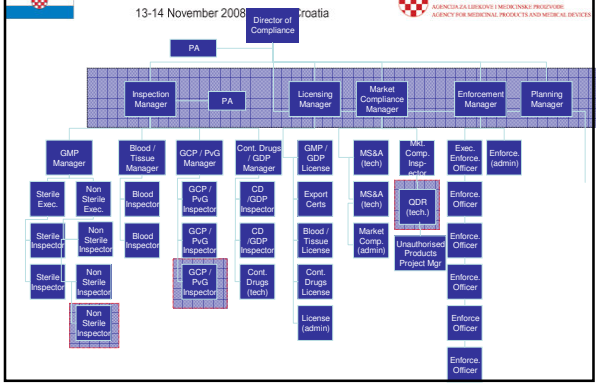

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Inspection Process

Notification	Inspection
• Date • Inspector • Requirements	• Quality System • Facility • Report of Deficiencies/Inspection Report
Closure	**Follow Up**
• Within 90 Days • Recommendation of granting of licence (New Application) • Issue of GMP Cert • Eudra GMP Update	• Response to inspection report -Address Deficiencies -Plan for Implementation of Corrective Actions -IMB Consideration

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National Legislation (1)

- **Medicinal Products (Control of Manufacture) Regulations 2007**
  http://www.dohc.ie/legislation/statutory_instruments/pdf/si20070539.pdf?direct=1
- Effective July 23rd 2007 - Consolidates requirements from
  -Title IV of Directive 2001/83/EC (as amended by Directive 2004/27/EC) which relate to the manufacture and importation of medicinal products for human use.

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National Legislation (2)

-Article 13 of Directive 2001/20/EC and **Chapter 3 of Directive 2005/28/EC** which relate to the manufacture and importation of investigational medicinal products.

-Directive 2003/94/EC which lays down the principles and guidelines in respect of manufacture of medicinal products (including investigational medicinal products) for human use.

-One set of manufacturing regulations for human medicines and IMPs

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National Legislation (3)

- **2001/82/EC - Veterinary Medicines**
  -Transposed into Irish law in European Communities (Animal Remedies) (No. 2) Regulations 2007 (superceded Regulations from November 2005)

  http://www.agriculture.gov.ie/legislation/SI2007/SI786-2007.pdf)

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Inspection Focus & Deficiencies (1)

- **Critical**
  A failure that indicates a significant risk that a product could or would be harmful to the patient, or a failure that has produced a harmful product
- **Major**
  A non critical failure which indicates a significant departure from GMP
- **Other**
  A deficiency which cannot be classified as either critical or major, but which indicates a departure from GMP

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Inspection Focus & Deficiencies (2)

3 Critical Deficiencies issued 2006-2008

-In 2 cases: A combination of multiple major deficiencies in EU GMP compliance resulting in lack of confidence in the quality management system

-In 1 case: Deficiencies in a number of areas impacting Sterility Assurance had a cumulative potential to lead to a significant risk of producing a product which is harmful to the veterinary patient.

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Inspection Focus & Deficiencies (3)

Overview of Major Deficiencies 2006-2008

Section of EU GMP Guide	**%**
Quality Management	24
Personnel	7
Premises & Equipment	17
Documentation	5
Production	34

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Inspection Focus & Deficiencies (4)

Overview of Major Deficiencies 2006-2008

Section of EU GMP Guide	**%**
Quality Control	12
Contract Manufacture & Analysis	0
Complaints & Recall	1
Self Inspection	0

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Inspection Focus & Deficiencies (5)

Overview of Major Deficiencies 2006-2008

- **Production**
  - -Inadequate process validation
  - -Demonstration that the manufacturing process is not adequately controlled
  - -Inadequate precautions to prevent mix-ups
  - -Demonstration of poor manufacturing practice
  - -Inadequate cleaning validation
  - -Inadequate control of starting materials

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Inspection Focus & Deficiencies (6)

Overview of Major Deficiencies 2006-2008

- **Quality Management**

-Inadequate Procedure for Product Release
Not apparent how it is ensured that the release procedure is in compliance with the Marketing Authorisation
Definition of responsibilities/procedure for product release poorly defined

-Non-conformance/deviations not reported

-Inadequate handling and investigation of non-conformances/ deviations

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Inspection Focus & Deficiencies (7)

Overview of Major Deficiencies 2006-2008

- **Quality Management**

-Inadequate handling of Change Control
Procedure not followed in all cases
Change Controls not adequately assessed with regard to validation requirements

-Absence of a system for performing Product Quality Reviews

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Inspection Focus & Deficiencies (8)

Overview of Major Deficiencies 2006-2008

- **Premises & Equipment**

-Standard of housekeeping, and finish and design of GMP areas not acceptable
Peeling paintwork, loose and flaking plaster, dead flies
Walls/ceilings not flush
Ledges on walls & doors
Gaps & holes in ceilings and walls of GMP areas
Floors not sloping to drain
Inadequate dust extraction

-Cleaning procedures not sufficient to prevent contamination/ cross contamination

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Inspection Focus & Deficiencies (9)

Overview of Major Deficiencies 2006-2008

- **Premises & Equipment**

Design of the manufacturing facility not adequate to ensure product manufactured in compliance with GMP

-Production did not occur in a logical order e.g. raw materials for processing were brought into the facility through a wash room area
-Design of the GMP areas not acceptable e.g. ceiling was not a sealed integral unit, processing pipe-work was not integrated into the walls
-Processing operations were conducted in an open environment with no added containment measures


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AGENCIJA ZA LIJEKOVE I MEDICINSKE PROIZVODE
AGENCY FOR MEDICINAL PRODUCTS AND MEDICAL DEVICES
• Thank-you to the Croatian Agency for Medical Products and Medical Devices & EMEA for the invitation
• Thank you for your attention
• Questions are welcome
• Queries on the GMP inspection programme are welcome and can be submitted to compliance@imb.ie