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*Active Pharmaceutical Ingredients*  
*IMB Inspection Program 2000-2007*

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# Today's Presentation

- Review of the IMB inspection program of API manufacturing facilities in the Republic of Ireland and abroad (2000-2007 inclusive)
- Deficiencies – overview of what the IMB observed
- Risks to supply chain & counterfeit



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# Legal Basis relating to APIs

- Directives 2001/83/EC ([human](#)) & 2001/82/EC ([veterinary](#))
- Amended by Directives 2004/24/EC & 2004/27/EC ([human](#)) & 2004/28/EC ([veterinary](#))
- 2001/83/EC (Article 46), 2001/82/EC (Article 50)  
Requirement for finished product manufacturers to 'use as starting materials only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials'
- Transposed into National legislation:

Medicinal Products (Control of Manufacture) Regulations 2007

European Communities (Animal Remedies) (No. 2) Regulations 2007



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# Authority to inspect API manufacturers

- 2001/83/EC (Article 111), 2001/82/EC (Article 80)
- The provision to allow Competent Authorities inspect the premises of active substance manufacturers:

‘The competent authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials,.....**whenever it considers that there are grounds for suspecting non-compliance** with the principles and guidelines of GMP’

- Currently, no requirement for API site to be authorised



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# EMA – grounds for conducting API inspections

- EMA API GMP Inspection Triggers document (2005):  
<http://www.emea.europa.eu/Inspections/GMPCompproc.html>
- Examples of when an inspection may be necessary:
  - (a) when **analysis of a sample of API** indicates a non-compliance with the specification or suitability for its use
  - (b) when a **report of a serious adverse reaction** and/or a **recall** of a medicinal product occurs when the quality of the API is implicated
  - (c) when **requested by the company**, seeking GMP certification



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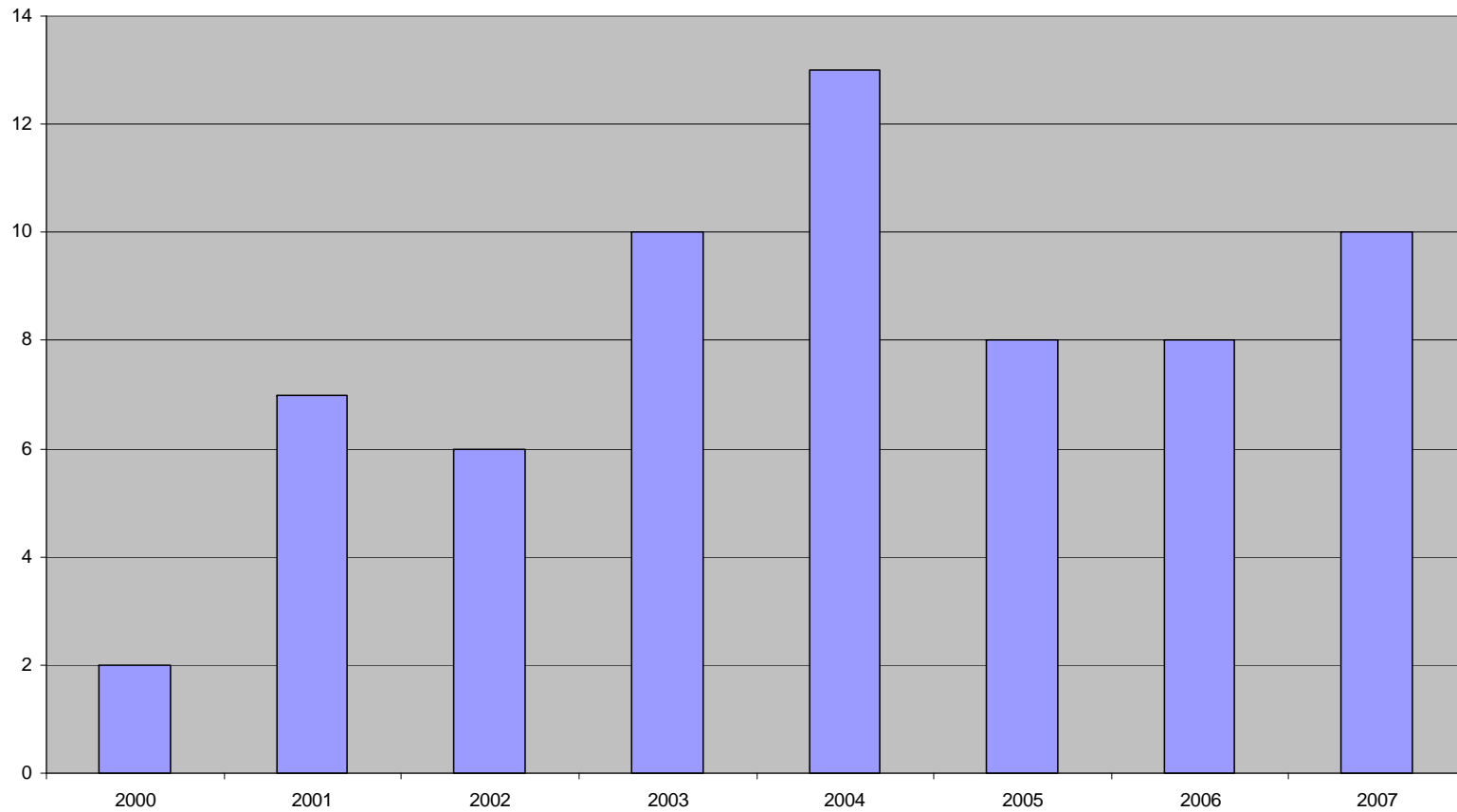
# History of API inspection program

- Commenced in the mid 1990s
- Limited number of API sites and IMB Inspectors
- Now, a rolling program of API inspections is in place
- 2 to 3 year frequency for 'routine' inspection
  - *See IMB Newsletter, Issue No. 29*
- Provision to conduct non-routine inspections:
  - Significant change to premises
  - Introduction of new API, technology, equipment



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# Increase in the number of inspections



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# Increase in the inspection duration\*

Year	No. of inspections	Average (days)*
• 2000:	2	2
• 2001:	7	2
• 2002:	6	3
• 2003:	10	4
• 2004:	13	4
• 2005:	8	4
• 2006:	8	4
• 2007:	10	4

- Duration: Minimum (2 days), Maximum (5 days)



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# Review period 2000-2007

- Number of inspections performed: 64
- Number of API sites inspected: 27
- Total number of deficiencies: 977
- Average per inspection: 15
- Critical: 1 (0.1%)
- Major: 37 (3.8%)
- Other: 939 (96.1%)



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# Breakdown of Total Major Deficiencies

- Quality Management 10
- Personnel 1
- Buildings & Facilities 12
- Process Equipment 2
- Documentation & Records 2
- Production & IPCs 3
- Storage & Distribution 1
- Validation 5
- Rejection & Reuse 1



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# Breakdown of Major Deficiencies by Year

Year	No. of 'Major'	Av. per inspection
• 2000:	2	1
• 2001:	0	0
• 2002:	1	< 1
• 2003:	17	2
• 2004:	11	< 1
• 2005:	1	< 1
• 2006:	3	< 1
• 2007:	2	< 1
• Overall on average < 1 'major' per inspection		



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# Breakdown of Other Deficiencies

• Quality Management	122
• Personnel	45
• Buildings & Facilities	125
• Process Equipment	94
• Documentation & Records	154
• Materials Management	26
• Production and IPCs	48
• Packaging & Labelling	19
• Storage & Distribution	15
• Laboratory Controls	143
• Validation	80
• Change Control	27
• Rejection & Reuse	7
• Complaints & Recall	17
• Contract Manufacturers	17



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# Breakdown of Other Deficiencies by Year

Year	No. of 'Other'	Av. per inspection
• 2000:	25	13
• 2001:	33	5
• 2002:	73	12
• 2003:	199	20
• 2004:	237	18
• 2005:	88	11
• 2006:	141	18
• 2007:	143	14
• Overall on average ~ 15 'other' per inspection		



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# Variable factors

- API manufacturing site:
  - size of the facility
  - nature & complexity of manufacturing processes
- IMB Inspection Team:
  - number of inspectors & assessors, if applicable
  - duration & focus of inspection – routine or directed
- Classification of deficiencies
  - GMP Guide - overlap of areas e.g. ‘documentation’
  - Grouping of ‘other’ deficiencies to a ‘major’ deficiency



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# Analysis of Deficiencies

- 5 headings chosen for analysis purposes
- 1. Quality Management System
  - (Quality Management, Personnel, Change Control, Documentation & Records, Complaints & Recall, Packaging & Labelling, Rejection & Re-use)
- 2. Premises & Equipment
  - (Buildings & Facilities, Process Equipment, Materials Management, Storage & Distribution)
- 3. Production
- 4. Laboratory Controls
- 5. Validation



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# % Breakdown of Major Deficiencies

	<u>Number</u>	<u>%</u>
• Quality Management	14	38
• Premises & Equipment	15	41
• Production	3	8
• Laboratory Controls	0	0
• Validation	5	14
• No Major deficiencies under 'Laboratory Controls'		



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# % Breakdown of Other Deficiencies

	<u>Number</u>	<u>%</u>
• Quality Management	408	43
• Premises & Equipment	260	28
• Production	48	5
• Laboratory Controls	143	15
• Validation	80	9

- Most common area is Quality Management
- Underpins all aspects of the manufacturing organisation



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# Examples of Major deficiencies

- **1. Quality Management (38%)**
- Management of process deviations
- Identification of root cause
  - Human error ?
  - Implementation of appropriate corrective actions
  - Assessment of impact on related batches
- Risk Management
  - Develop a hypothesis but neglect to test the theory
  - Reflect on decisions and challenge decision
  - *See IMB Newsletter, Issue No. 29*



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# Risk management ?



- Neville Chamberlain declaring 'Peace in our time' following a meeting with Adolf Hitler, *30 September 1938*



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# Examples of Major deficiencies (continued)

- **2. Premises & Equipment (41%)**
  - Design or set up of equipment presents a risk of contamination and/or cross-contamination of API
- **3. Production (8%)**
  - As per No. 2 above – cross-over of GMP Guide



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# Examples of Major deficiencies (continued)

- **4. Laboratory Controls (0%)**
  - No major deficiencies identified during review period
- **5. Validation (14%)**
  - Cleaning validation absent or not appropriate
  - Process not supported by validation



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# Examples of Other deficiencies

- **1. Quality Management (43%)**
- Annual Product Reviews incomplete:
  - incomplete analytical testing data
  - overall conclusions / status not included
- SOPs not reflective of actual practice
- SOPs / forms missing key data
- Technical Agreements absent or unclear



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# Examples of Other deficiencies (continued)

- **2. Premises & Equipment (28%)**
  - Gowning procedures absent from GMP areas
  - Decrease in standard and finish of area e.g. loose paint
  
- **3. Production (5%)**
  - SOPs describing production activities were unclear
  - HVAC pressure gauges not working effectively
  - Observation of inappropriate material in production



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# Examples of Other deficiencies (continued)

- **4. Laboratory Controls (15%)**
  - No evaluation of shelf-lives for analytical reagents
  - Calibration activities not conducted as per Ph. Eur.
  
- **5. Validation (9%)**
  - Lack of validation or consideration to conduct validation
  - Protocol not identifying critical parameters
  - Lack of implementation of validation report recommendations



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# How does IMB programme compare ?

- EMEA report on inspections: 1995-2005
- Inspections performed in both EEA & Third Country  
[Reference document - EMEA/INS/GMP/23022/2007](#)

	<u>IMB</u>	<u>EMEA</u>
• No. of inspections:	64	119
• Average per inspection:	15	17
• % Critical	0.1	1.7
• % Major	3.8	15.5
• % Other	96.1	82.8



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# Inspection Findings (EMEA)

- Manufacturing not in compliance with GMP
- Manufacturing outside of the Marketing Authorisation
- Significant changes to a facility
- Use of Raw Materials of questionable source e.g. Heparin
- Traceability ~ brokers, agents & traders



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# Roles & Responsibilities

- The mission of the Irish Medicines Board is:  
**‘to protect and enhance public and animal health through the regulation of medicines, medical devices and healthcare products’**
- Responsibility of Industry towards protecting public and animal health
- Material of questionable source entering the legitimate supply chain = counterfeit material
- Counterfeit material = risk to public and animal health



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# Safeguarding the supply chain

## Part II of EU GMPs

- 6.3: Requirement to maintain records of suppliers
- 7.11: System in place to evaluate suppliers of critical materials
- 7.12: Materials should be purchased against an agreed specification, from supplier(s) approved by the quality unit(s).
- 7.14: Changing the source of supply of critical raw materials should be treated according to Section 13, Change Control
- 7.3: Sampling and Testing of Incoming Production Materials



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# Next Steps

- Continued inspection of Irish based API manufacturing sites
- Continued participation in EMEA / EDQM non-EEA based inspections
- European Commission Proposals (as outlined earlier)
- Exchange of information is vital !!
- EudraGMP
- Pilot API inspection Programme



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# API Inspection Pilot Programme

- **Reference document:** 'Outline of a pilot project to rationalise international GMP inspection activities'
- <http://www.emea.europa.eu/Inspections/WhatsNew.html>
- Pilot group established comprised of:
  - EU Ireland, UK, Germany & France (also EMEA/EDQM)
  - Non-EU FDA & TGA
- Shared resources for targeted API inspection of non-EEA sites
- Commencement – Q4 2008



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# Conclusions !

- Only 1 Critical observation: company addressed.
- 66% of inspections result in no Critical/Major observations.
- There was 1 recall of finished product (2000-2007) in which the quality of API was implicated.
- Major deficiencies focus on:
  - (a) Quality Management System
  - (b) Design & Maintenance of premises & equipment
- Increased focus on the use of risk management
- Increased focus on supply chain activities



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# Acknowledgements

- Special thanks to the Compliance staff of the IMB.
- Thank you for listening.
- Any Questions ?



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