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General GMP Update

23rd October 2008 – Crowne Plaza Hotel

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Agenda

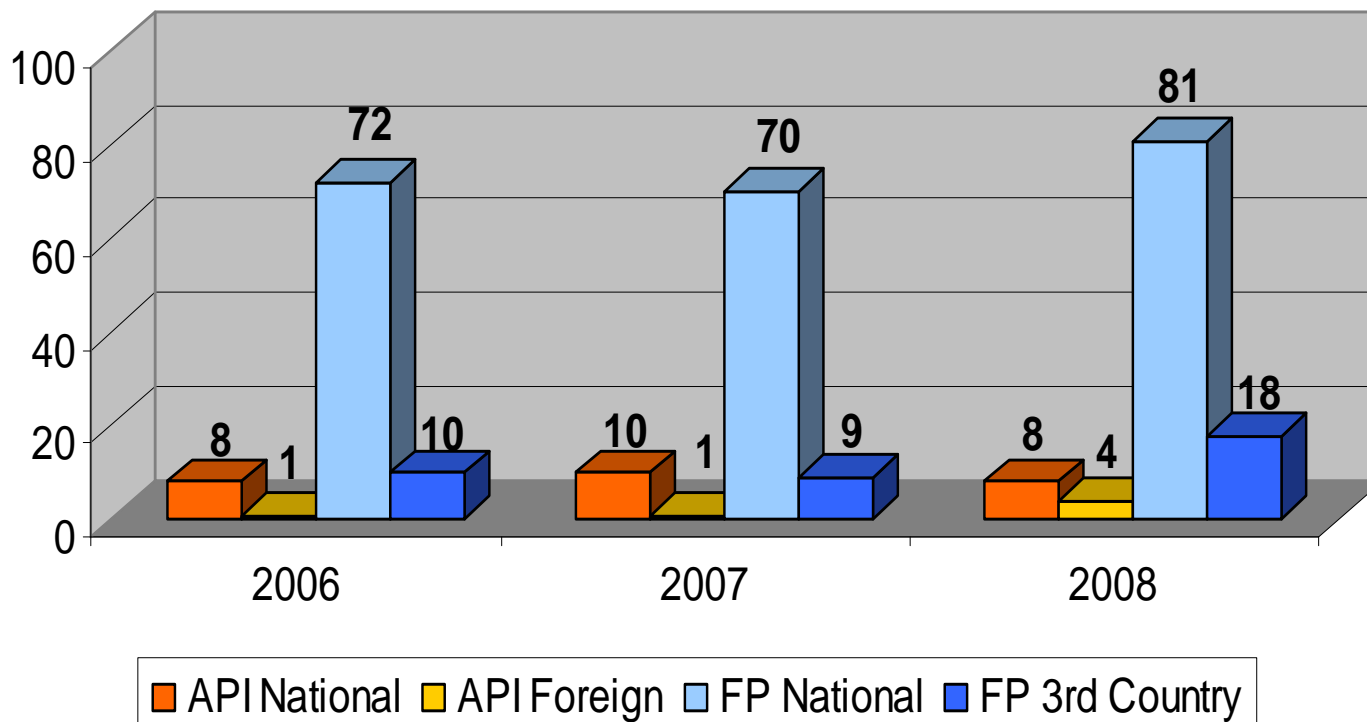
1. Overview of inspection statistics
2. Main changes over past two years
3. General EU Update
4. Joint Audit Programme
5. Manufacturer's Authorisation
6. Information on active substances supplied from outside EEA



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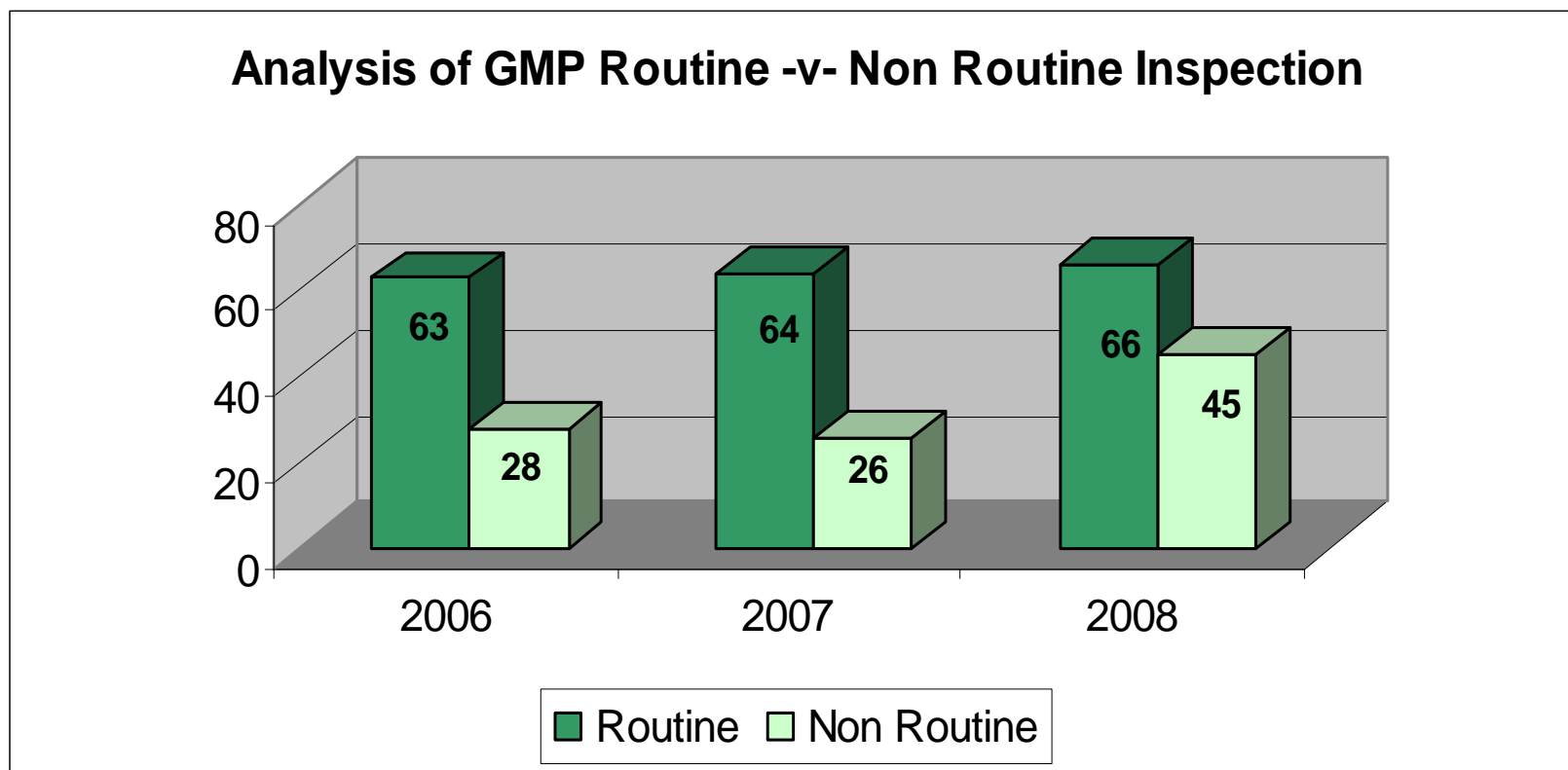
Overview of GMP Inspection Programme (1)

Number of site inspections 2006-2008



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Overview of GMP Inspection Programme (2)



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Legislation Changes (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 these directives.

- **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.
- **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

Legislation Changes (2)

Highlighting of specific aspects of SI 539 of 2007

- GMP for Active Substances
- GMP certification

- Definition of “exempt” medicinal product
- Importation of “exempt” products by authorised manufacturers only (Doctors / Dentists can no longer import)
- QP not obliged to certify batches of manufactured or imported ‘exempt product’



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Legislation Changes (3)

Application Process for Manufacturer's Authorisation

Applicant can make representations where it is proposed to grant authorisation;

- Other than in accordance with the application
- Subject to carrying out certain obligations

Renewals of Manufacturer's Authorisation

- Not required for manufacturer's authorisation for human medicines or IMPs



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Legislation Changes (4)

Suspension

- Immediate suspension for safety reasons (up to 3 months)
- Company invited to make representations
- Suspension may apply to some activities or all activities



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Legislation Changes (5)

Authorisation Conditions

- Conditions listed separately for Manufacturers and Importers
- Compliance with GDP required
- Exempt product notification scheme for imported products
- Records kept for 5 yrs from date of QP certification (previously DOM)



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Legislation Changes (6)

Manufacture of Herbal / Homoeopathic Medicines

- QPs (transitional) from other MS eligible to apply for QP status here.
- Provision of transitional arrangements for QPs at Herbal Manufacturers
- Makes provision for preparation of herbal or homeopathic medicine by non-industrial process, without an authorisation
 - labelling important (no brand name, no recommendations for use)



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Legislation Changes (7)

Traditional Herbal Medicines

2001/83EC amended by 2004/24/EC

Registration Scheme – phased implementation up to April 2011

Manufacture / Wholesale authorisation requirements applicable now



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Legislation Changes (8)

- 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>)

- One renewal required after first issue of licence.



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Changes to GMP Guidelines (1)

Chapter 1, Quality Management,

- Inclusion of Quality Risk Management as a requirement for an effective overall system of Quality Assurance
- came into force 1st July 2008

(Part II – Similar section on QRM currently out for consultation until 31st Oct 2008)

Annex 20 ‘Quality Risk Management’ (as per ICH Q9),

- published Feb 08 and came into force March 08
- offers some optional tools for QRM



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Changes to GMP Guidelines (2)

Chapter 3 & 5, 'Premises & Equipment' and 'Production':

- revision required to deal more fully with the requirements for 'dedicated facilities
- discussion still ongoing at EU level
- EMEA published a statement in January 08
- QRM Vs Defined list of products or combination of both
- Toxicological / Pharmacological expertise sought
- Outcome of this work is yet to be finalised

Chapter 5

- Discussions also ongoing with regard to update of the paragraphs on vendor approval in the light of new requirements for active substances.



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Changes to GMP Guidelines (3)

Annex 1, 'Manufacture of Sterile Medicinal Products';

- number of amendments including particle counting and capping
- coming into force 1st March 2009
- capping requirements in force by 1st March 2010
- see presentation by Greg McGurk



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Changes to GMP Guidelines (4)

- Annex 2, 'Manufacture of Biological Medicinal Products',

Significant update to this Annex taking into account GMP for active substances and the increased range of biological products.

Consultation period completed in March 08 and final draft being prepared.

- Annex 3 'Manufacture of Radiopharmaceuticals'

- Deadline for coming into operation 01 March 2009.

- The annex has been revised in the light of new GMP requirements for active substances used as starting materials (GMP Part II) and updated for all relevant aspects of GMP for radiopharmaceuticals.



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Changes to GMP Guidelines (5)

Annex 6, 'Manufacture of Medicinal Gases'

Clearer division between active substance manufacture and medicinal product manufacture.

- Consultation period finished
- Final draft to be presented to the EU Commission for final adoption.



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Changes to GMP Guidelines (6)

Annex 7 'Manufacture of Herbal Medicinal Products'

- published September 2008
- comes into force on 1st September 2009
- incorporates GMP requirements for actives used as starting materials
- guidance provided on the transition between Good Agriculture and Collection Practice (GACP), GMP Part II and GMP Part I requirements.
- timely as it coincides with implementation of registration scheme for traditional herbal medicinal products



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Changes to GMP Guidelines (7)

Annex 11 'Validation of Computerised Systems' and Chapter 4, Documentation

Significant revision of Annex 11

Significant revision of Chapter 4 - A number consequential updates arising from Annex 11 and other updates.

Public consultation up to end of October 2008



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Changes to GMP Guidelines (8)

Annex 13 – Manufacture of IMPs

Update to include

- Clarification on division of QC & Production responsibilities for small facilities
- Requirements with regard to Reference and Retention Samples
- Clarification of the two step release process
- Public consultation up to end of Oct 08



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General EU Update (1)

Compilation of Community Procedures for GMP inspectorates

‘A model for risk based planning for inspections of Pharmaceutical Manufacturers’

- Early change to two year (authorised manufacturers) & three year (active substance manufacturers) 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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General EU Update (2)

QP Discretion

- Particular concern of manufacturers
- IMB initiative via HMA late 2005
- Reflection Paper published March 2006
- Comments received at EMEA
- Next steps ?
 - Revise Reflection Paper (ongoing)
 - Revise Annex 16
 - Await publication of revised variations regulation (text finalised)



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General EU Update (3)

European Commission' Better Regulation Initiative

- New Variations Regulation on Commission website
- aim to provide a more flexible approach to variations
- Member States have approved the new Commission Regulation
- Likely to come into force Qtr 4 2009
- Increased flexibility for MA holders and manufacturers for minor changes
- Annual reporting system for minor changes



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General Update (4)

Atypical Actives

- Not a typical pharmacologically active compound
- May be more routinely used as an excipient or a foodstuff (eg citric acid, honey)
- GMP declaration by QP required with regulatory submissions in EU
- Discussion at Interested Parties meeting at GMDP IWG in Sep 07
- difficulty for certification against EU GMP
- Q & A to be published on EMEA website



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Joint Audit Programme (1)

- Audit of Competent Authorities
 - EU Compilation of Procedures
 - assessment & harmonisation of EU inspectorates
 - may also be used to support MRAs and PIC/S membership

JAP at IMB – July 2008

- 3 Auditors at the IMB for one week
- focus GMP inspections, Sampling and Analysis, Market Compliance and aspects of Enforcement



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Joint Audit Programme (2)

- Observation of GMP inspection process
- Review of legislation and quality system against defined markers
- No critical or major deficiencies identified
- A number of other deficiencies noted
- Response to the report has been sent to the auditors



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Notification of Changes

- Notification of site changes
- Prior notification of any changes to any of the particulars supplied in the application.
(SI 539 of 2007 – Schedule 2)
- Many points from the application are covered on Manufacturer's Authorisation
 - Address of manufacturing site
 - General classification of product and dosage forms
 - Activities (manufacture, packaging, importation, batch release, distribution)



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Notification of Changes

- Some changes not captured at Authorisation level:
 1. Prior notice of changes to equipment or facilities where there is no change to details already present on the Manufacturer's Authorisation.
 - Many manufacturers do notify the IMB of intended changes even where the activity would not have impact on the authorised activities.
 - Inspection may or may not be required.



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Notification of Changes

Other information supplied in the application

- Activities at the site other than manufacture of medicines.
- CV details of the QP & persons responsible for Production and Quality Control
- Arrangements for storage & identification of materials, stock rotation, maintenance of records, reference & retention samples, recall



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Notification of Changes

Site Master File

- contains much of the application information
- often only updated prior to inspection
- could be used as a mechanism for prior notification of changes
- Advance notification period should reflect the complexity and extent of the change



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Manufacturer's Authorisation (1)

- EMEA format (Compilation of Procedures)
- IMB has committed to generating authorisations in the revised format
- Electronic system developed
- Transfer of the information to EudraGMP database (MA and GMP Certificate details)
- Company access to electronic version on IMB website
- Public access to EudraGMP – discussions ongoing at EU level as to what level of access will be granted.



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Manufacturer's Authorisation (2)

Your assistance is requested !

86 Manufacturer's Authorisations for Human Medicines

45 Manufacturer's Authorisations for IMPs

26 Manufacturer's Licences for Veterinary Medicines

11 Laboratory Approvals

Total No. of Authorisations = 168

- Existing licence data inputted for many authorisations/licences
- Process of validating information with the manufacturer



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Manufacturer's Authorisation (3)

Advantages with this system :

- Access to the information for Manufacturers by logging onto the website
- Electronic submission of variations
- Easier management of licence details and submission of variations
- Data on system used to generate final authorisation document (EU format)



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Pilot Project Inspection

- Cooperative project between regulatory authorities (including EU and FDA)
- A number of authorities participating (including the IMB)
- Focussed on inspection of active substance manufacturers
- Sharing of inspection plans
- Sharing of inspection resources
- Evaluation of pilot phase - extend the scope ?



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Imported Active Substances (1)

- Irish Active Substance Manufacturers
 - No requirement for authorisation
 - Routine inspection of sites for maintenance of GMP certification (voluntary)

Active substance manufacturers in other EEA countries

- Many are GMP certified or inspection by local competent authority or inspection could be requested via ‘triggers*’ procedure. * Ref EU Compilation of Community Procedures

MRA Countries – discussions ongoing with regard to active substances being covered within the scope



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Imported Active Substances (2)

- IMB wants to collect information on active substances supplied from outside the EEA.
- Information requested from manufacturers of medicinal products (human / veterinary).
- This information needs to be maintained to reflect current activities.
- Looking at an electronic means for maintaining this information



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Imported Active Substances (3)

- Information required from each manufacturer of medicinal products
 - Name of the active substance(s) imported from countries outside the EEA.
 - Name of the manufacturer of each imported active substance.
 - Name of any broker/agent/trader involved in supply chain for each imported active substance.
 - Name of importing site *
 - Name of any sites involved in packaging* or labeling* of the active substance.

*also considered manufacturers of active under the amended directives 2001/82/EC and 2001/83/EC