IRISH MEDICINES BOARD

Regulatory Update

IMB Information Day

Crowne Plaza Hotel, Santry 27th September 2012

Paul Sexton
GMP Manager

Content

1. Legislation
2. Revisions to EU GMP Guidance
3. MIA / GMP Certificates
4. Inspection Planning
5. International Co-operation

IRISH MEDICINES BOARD

Legislation

IRISH MEDICINES BOARD

Legislation

Falsified Medicines Directive 2011/62/EU

- amends Directive 2001/83/EC (Human Medicines)

- prevention of the entry of falsified medicines into the legal supply chain.

- To be transposed into Irish legislation by 02.01.13

- Most measures to be implemented by 02.01.13

- Longer period for aspects dependent on delegated acts and implementing measures

IRISH MEDICINES BOARD

Legislation

Falsified Medicines Directive - Implications

- API Manufacturers in EU (registration)
- API Importers in EU (registration)
- API Distributors in EU (registration)

- Medicinal Product Manufacturers
  - Mandatory audits of API sites
  - Risk assessment of excipients
  - Use of imported active substances
  - Application of safety features

IRISH MEDICINES BOARD

Legislation

Falsified Medicines Directive – Implications

- Wholesalers of medicinal products
- Brokers of medicinal products (Registration)
- Competent Authorities
- European Medicines Agency

IRISH MEDICINES BOARD

Legislation

Principles and Guidelines of GMP for APIs in Medicinal Products (Human)

Guidelines in existence for some time (ICH Q7A)

Legal force to the GMP principles for APIs

Concept paper published 20.01.12

- Proposed extension of GMP directive (2003 / 94/EC) to cover APIs also
- Some provisions of 2003/94/EC not applicable eg MIA requirement, QP requirements, MA references, IMP requirements
- Specific provisions for APIs may be added

IRISH MEDICINES BOARD

Legislation

Irish legislation to be updated

- IMB Act
- Control of Manufacture Regulations
- Control of Wholesale Regulations
- Control of Placing on the Market Regs.
- Prescription and Control of Supply Regs.

IRISH MEDICINES BOARD

Revisions to GMP Guidance

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Chapter 1 – Pharmaceutical Quality System

Revised chapter now published in EudraLex Vol 4

Coming into force – January 31st 2013

Chapter 2 – Personnel

Chapter 2 text being finalised

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Chapters 3 & 5 – Premises & Equipment / Dedicated Facilities

GMP guidance text has been drafted

Safety Working Party (at EMA) is drafting guidance on setting health based exposure limits for use in risk identification in the manufacture of medicinal products in shared facilities.

(Parallel Session 2A)

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Chapter 5 – Production

1. Revision of guidance on supply of starting materials- traceability of active substance manufacture

   (QWP Template for QP Declaration for APIs)

2. Reduced testing – criteria defined for implementation of reduced testing

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Chapter 6 – Quality Control

Revision to introduce guidance on transfer of analytical methods

Opportunity was used to look at some other aspects of the text in the chapter.

Anticipate public consultation later in 2012

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Chapter 7 – Outsourced Activities

Revised chapter now published in EudraLex Vol 4

Coming into force – 31st January 2013

Wider scope as reflected in new title for the chapter

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Chapter 8 – Complaints and Product Recall

Concept Paper was out public consultation (ended 12.07.11)

ICH Q10 terminology

Clarification of responsibilities of MAH and MIA holder for reporting defects & their investigation.

Focus on root cause analysis & QRM approach

Anticipate public consultation later in 2012

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Annex 2 Manufacture of biological active substances and medicinal products for human use

Revised chapter now published in EudraLex Vol 4

Coming into force – 31.01.13

Significant revision of the guidance

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Annex 15 Qualification and Validation

Concept Paper – drafted

Emphasis on process knowledge - ICH Q8, Q9 & Q10

Guideline on Process Validation

Issued for public consultation until 31.10.12

Available on EMA website

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125399.pdf

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Annex 17 Parametric Release

Concept Paper – drafted

Wider application than parametric release associated with sterility testing.

Emphasis on process knowledge

Guideline on Real Time Release Testing

Coming into effect 01.10.12

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125399.pdf

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Annex 16

Concept Paper

-Developed

-Adopted

-Released: October 2011

DONE!

Draft Text

- Prepare
- Agree
- Release: December 2012

In Progress

Final version

Prepare: Q4 2013

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Revision of Annex 16

- QPs' knowledge about manufacturing site(s)
- Should a QP personally audit these sites and API producers?
- Site where products are physically imported *vis-à-vis* site for batch certification
- Deviations and compliance with the MA
- Sampling location for imported batches

IRISH MEDICINES BOARD

Revision of EU GMP Guidelines

Revision of Annex 16

- Falsified Medicines Directive 2011/62/EC

- Introduces a new obligation for QPs to check that safety features are present on packs

- This won't apply until at least 2017;

  3 years after the publication of 2° legislation (delegated act)

IRISH MEDICINES BOARD

Revision of EU GMP Guidance

Guidance for Distribution of Active Substances

- Required under Falsified Medicines Legislation
- Text has been drafted
- Broadly similar to requirements for medicinal products

IRISH MEDICINES BOARD

Other Guidance

Audit of Active Substance Manufacturers

- Expectation under GMP but will be a legal requirement under FMD.
- Expectations of inspectors in relation to audits was raised at an interested parties meeting previously.
- Q&A on this under preparation.

Risk Assessment of Excipients by Manufacturers

- FMD requirement
- Guidance under preparation

IRISH MEDICINES BOARD

MIA / GMP Certificates

IRISH MEDICINES BOARD

MIA / GMP Certificates

- **EudraGMDP**
- New name to include wholesaling activities
- Launch in Jan 2013
- New activities on the database
  - Wholesaler's Authorisations
  - Wholesaler's GDP certificates
  - Registration of API manufacturers
- Changes to MIA format

IRISH MEDICINES BOARD

MIA / GMP Certificates

- **MIA (today)**
- Many operations under one dosage form entry
- 1.2.1.13 Tablets (includes manufacture of dosage form, primary packaging, secondary packaging, batch certification)
- 1.2.2 Batch certification **only**
- 1.5 Packaging **only**

IRISH MEDICINES BOARD

MIA / GMP Certificates

- **MIA (effective January 2013)**
- Single operation covered for each entry
- 1.2.1.13 Tablets (**processing operations** for the dosage form)
- 1.2.2 Batch certification ~~(only)~~
- 1.5 Packaging ~~(only)~~
- New category of biological products – Tissue engineered products

IRISH MEDICINES BOARD

MIA / GMP Certificates

- **MIA Interpretation Document**
- document in preparation
- harmonised interpretation of what entries on an MIA / GMP cert
- important for assessors, inspectors and industry
- IMB project to migrate current MIAs to new format to start in January 2013

IRISH MEDICINES BOARD

MIA / GMP Certificates

Variation Submissions

- Number of variations processed during 2011
- 908 Total Received
- 431 Admin
- 477 technical (inspection deemed necessary for 19 variations)
- IMB guidance document[1] on requirements for variation submissions
- Incomplete submissions cannot be validated
- Results in delays

[1] http://www.imb.ie/EN/Publications/Publications/Application-for-variation-of-a-manufacturers-or-wholesalers-authorisation--licence.aspx

IRISH MEDICINES BOARD

MIA / GMP Certificates

Changes to GMP Certificate (effective January 2013)

- Similar changes to manufacturing operations as per MIA
- New section on manufacturing operations for active substances
- More descriptive detail on manufacturing operations

3.1 Manufacture of Active Substances by Chemical Synthesis

- *3.1.1 Manufacture of active substance intermediates*
- *3.1.2 Manufacture of crude active substance*
- *3.1.3 Salt formation / Purification steps : <free text> (e.g. crystallisation)*
- *3.1.4 Other <free text>*

IRISH MEDICINES BOARD

Inspection Planning

IRISH MEDICINES BOARD

Inspection Planning

Risk Based Inspection Planning
Tool developed by PIC/S group

- Used for planning routine inspection frequency of API and finished product manufacturers

- 2 risk factors form the basis of the tool
- i) **Intrinsic Risk** - factors include complexity of the site, nature of the products, product criticality

- ii) **Compliance Risk** –factors include inspection history

IRISH MEDICINES BOARD

Inspection Planning

Risk Based Inspection Planning

- Scope and duration of inspection considered
- New information also can be taken into account
  - Significant changes at the site
  - Market Compliance issues

- IMB trial carried out with the tool
- Overall – positive result
- Assessing product criticality may require information on market share etc.

IRISH MEDICINES BOARD

Inspection Planning

Planning Module in EudraGMDP

- focus on sharing of inspection resources for third countries
- new inspection planning module being incorporated into EudraGMDP
- MS can enter sites which it intends to inspect and the dosage forms to be covered
- Other MS can search the planned inspections and request inspection of other areas / dosage forms

IRISH MEDICINES BOARD

International Co-operation

IRISH MEDICINES BOARD

International Co-operation

- **API inspections**
- Pilot API inspection programme (Dec 08–Dec10)
- Small number of authorities (FDA, TGA, EU (5 Member States), EDQM)
- Sharing of inspection plans “Master List”
- Conclusion – overall considered positive
- “Master List” is still maintained includes more EU participants
- Confidentiality agreements between members

IRISH MEDICINES BOARD

International Co-operation

Medicinal Products Inspections

- 2009 - Initiative for joint inspections EU / FDA
- Related to new products / new technologies
- Dec 2011 – Joint EMA / FDA paper
- “Confidence-building” to “Reliance upon”
- Focus on routine inspections (CAPS)
- Deferring or waiving inspection
- Criteria defined
- Applies to previous inspected sites
- History of satisfactory compliance
- Final decision with Supervisory Authority

IRISH MEDICINES BOARD

International Co-operation

- Reporting of Serious Non Compliance by non EU non MRA authorities

- Procedure for included in Compilation of Community Procedures (effective end Nov 2012)
- Could result from 3rd country authority inspections or any other sources
- Dissemination of the information and follow up

IRISH MEDICINES BOARD

International Co-operation

- **MRAs**
- MRAs – no change (Switzerland, Canada, Japan, Australia, New Zealand)
- ACCA with Israel – not yet active

International GMP Summit

Second meeting in Washington (Sept 2012)

- **PIC/S**
- Involvement of non EU PIC/S members in development of EU GMP Guide
- APIs Expert Circle meeting in Washington
- Training of inspectors

IRISH MEDICINES BOARD

Thanks for your attention

Questions

?

IRISH MEDICINES BOARD