



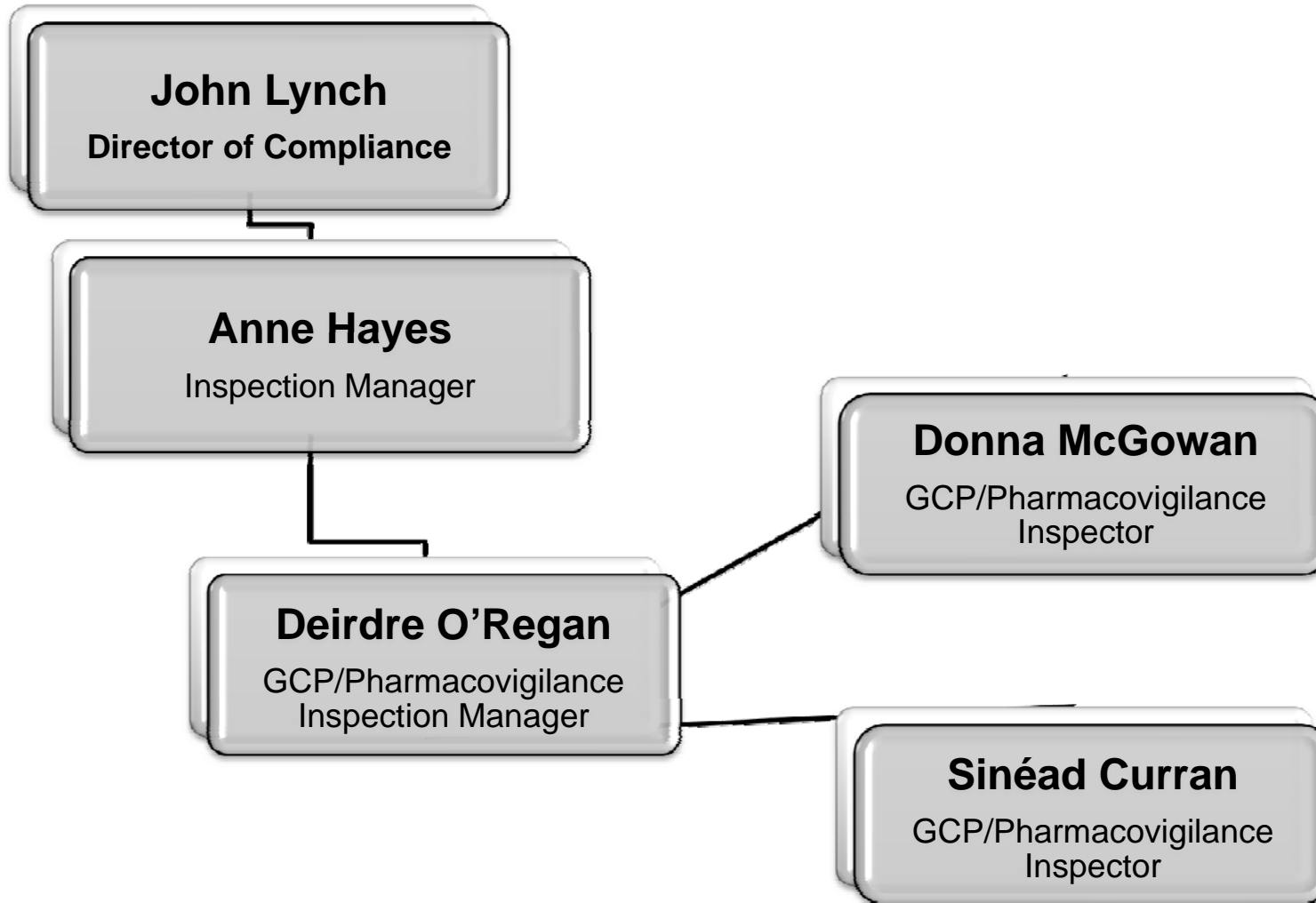
IRISH MEDICINES BOARD

Overview of the IMB's Approach to Inspection of Good Clinical Practice

GCP Seminar Dublin, 27th January 2010

Deirdre O'Regan
GCP/Pharmacovigilance
Inspection Manager

Introductions/Organisation



IRISH MEDICINES BOARD

Agenda

- Aims of the GCP Seminar
- Inspector Responsibilities
- Overview of Legislation and Guidance
- GCP Inspection References
- Scheduling GCP Inspections
- GCP Inspection Process



IRISH MEDICINES BOARD

Agenda contd.

- Classification of Inspection Findings
- Inspection Follow-up
- GCP Inspection History
- Summary of GCP Inspection outcomes 2007, 2008, 2009

- Aims of the GCP seminar



IRISH MEDICINES BOARD

Aims of the GCP Seminar

- Focus on investigator site responsibility (Section 4 of ICH GCP)
- Focus on areas of greatest risk
 - Legislative requirements
 - Expectations
 - Inspection findings



IRISH MEDICINES BOARD

Inspector Responsibilities



- Protection of public health
- Ensure that all parties involved in a clinical trial adhere to relevant legislation and guidance



IRISH MEDICINES BOARD

Overview of Legislation

- **Directive 2001/20/EC**
 - Implemented nationally into S.I. 190 of 2004, May 2004
 - Amended S.I. 878 of 2004, December 2004
- **Directive 2005/28/EC**
 - Implemented nationally into SI 374 of 2006, July 2006
- **Regulation (EC) No. 1394/2007**
 - Amended S.I. 1 of 2009, January 2009
- **Guidance Documents**



IRISH MEDICINES BOARD

Legislation & Guidance Documents

- EUDRALEX- Volume 10 Guidelines for Clinical Trials

“The rules governing medicinal products in the European Union” contains guidance documents applying to clinical trials.

- Chapter I : Application and Application Form
- Chapter II : Monitoring and Pharmacovigilance
- Chapter III : Quality of the Investigational Medicinal Product
- Chapter IV : Inspections
- Chapter V : Additional Information
- Chapter VI : Legislation

http://ec.europa.eu/enterprise/sectors/pharmaceuticals/documents/eudralex/vol-10/index_en.htm#h2-chapter-ii:-monitoring-and-pharmacovigilance



IRISH MEDICINES BOARD

- Vol 1: Legislation Human
- Vol 2: Notice to Applicants Human
- Vol 3: Guidelines Human
- Vol 4: GMP Human & Veterinary
- Vol 5: Legislation Veterinary
- Vol 8: MRL Veterinary
- Vol 9: Pharmacovigilance Human & Veterinary
- Vol 10: Clinical Trials
- ▶ EudraLex on CD Version 21 - September 2009
- Vol 6: Notice to Applicants Veterinary







EudraLex - Volume 10 Clinical trials guidelines

On this page:

- [Chapter I: Application and Application Form](#)
- [Chapter II: Monitoring and Pharmacovigilance](#)
- [Chapter III: Quality of the Investigational Medicinal Product](#)
- [Chapter IV: Inspections](#)
- [Chapter V: Additional Information](#)
- [Chapter VI: Legislation](#)

Volume 10 of the publications "The rules governing medicinal products in the European Union" contains guidance documents applying to clinical trials.

Chapter I: Application and Application Form

- [General information](#)  [375 KB] (July 2006)
- [Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial](#)  [334 KB] (revision 2 of October 2005)
 - [Annex 1: "Clinical trial application form"](#)  [226 KB] (revision 2 of October 2005)
 - [Annex 2: "Substantial Amendment Form"](#)  [136 KB] (revision 2 of October 2005)
 - [Annex 3: "Declaration of the end of the trial"](#)  [104 KB] (revision 2 of October 2005)
 - [Annex 1 revised](#)  [86 KB] (revision 4 of December 2009)

GCP Inspection References

- Clinical trials are inspected against:
 - S.I. 190 2004 (amendment S.I. 878, 2004), SI 374 of 2006, S.I.1 of 2009
 - Guidelines e.g.:
 - Note for Guidance on Good Clinical Practice: Consolidated Guideline (ICH Topic E6, Step 5) CPMP/ICH/135/95
 - EU Guideline for GMP: Annex 13: Manufacturing of Investigational Medicinal Products (Directive 2003/94/EC)
 - Commission guidelines
 - Study protocol
 - Clinical trial authorisation



IRISH MEDICINES BOARD

Scheduling GCP Inspections

- Current procedure for selection of sites for routine inspection:
 - Risk Based
 - Trial/sponsor/investigator/subcontractors not previously inspected
 - Geographical spread/therapeutic area
 - High level of clinical trial activity



IRISH MEDICINES BOARD

Scheduling GCP Inspections

- Who/what can be inspected? All locations where trial related activities are conducted e.g.
 - Sponsor/CRO sites
 - **Investigator sites**
 - Phase I facility
 - Clinical laboratory sites
 - IMP Manufacturing/packaging sites



IRISH MEDICINES BOARD

Scheduling GCP Inspections

- Types of Inspection:
 - Routine
 - Majority, to standard procedure
 - Follow-up
 - Corrective, preventive actions followed to closure
 - For-cause
 - Suspicion of fraud; the existence of adequate facilities; Clinical trials started without authorisation; Protocol amendments not approved by the IMB and/or Ethics Committee prior to enactment; Inadequate safety reporting; Inappropriate IMP manufacture, importation or management
 - European – co-ordinated by European Medicines Agency



IRISH MEDICINES BOARD

GCP Inspection Process

- Sponsor contacted 4 – 6 weeks prior to proposed inspection
- Inspection plan prepared
- Announcement letter & inspection plan to sponsor, including request for information
- Approx. 3 days at Investigator site



IRISH MEDICINES BOARD

GCP Inspection Process

- Opening meeting
 - Require Investigator to be present at opening and closing meetings
- Tour of facilities
- Review of clinical trial records
- SDV of approx. 10% of subjects
- SAE reporting



IRISH MEDICINES BOARD

GCP Inspection Process

- Searching, thorough & a learning experience!!
- Notify inspectees of major and critical deficiencies on an ongoing basis
- Closing meeting
 - Definition of deficiency classification provided
 - Inspection findings summarised
 - Deficiencies classified as far as possible (Input from IMB experts sometimes required)
 - Questions relating to findings answered
 - Follow-up activities explained



IRISH MEDICINES BOARD

Classification of Inspection Findings

- **Critical:** “Conditions, practices or processes that adversely affect the rights, safety or well being of subjects and/or the quality and integrity of data.”
- **Major:** “Conditions, practices or processes that might adversely affect the rights, safety or well being of subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles”
- **Minor:** “Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of subjects and/or the quality and integrity of data.”



IRISH MEDICINES BOARD

Inspection Follow-up

- Inspection follow-up re. major/minor deficiencies
 - Deficiency Summary Report - Day 15
 - Report issued - Day 28
 - Response to inspection report - Day 43
 - Correspondence, if necessary, Day 44 – Day 80
 - Inspection close out – Day 90



IRISH MEDICINES BOARD

Inspection Follow-up

- Possible actions arising from multiple major/critical deficiencies:
 - Deviations reviewed internally with representatives from Compliance and immediately after inspection
 - Recommendations regarding corrective actions/follow-up inspection
 - Possible meeting with sponsor regarding corrective action plan
 - Suspension of clinical trial activities



IRISH MEDICINES BOARD

GCP Inspection History

Year	GCP Sponsor	GCP Site	GCP Site: Non-Commercial	Phase I	EMA	Total
'04	0	4	5	1	1	11
'05	1	7	0	0	0	8
'06	4	10	1	1	0	16
'07	1	8	1	2	2	14
'08	0	12	1	0	2	15
'09	0	10	6	1	7	24
Total	6	51	14	5	12	88

D

Summary of GCP Site Inspection Outcomes 2007, 2008, 2009

	Critical Deficiencies	Major Deficiencies
Protocol Compliance	69.6%	19.1%
Informed Consent	-	19.1%
Safety	17.4%	15.6%

Aims of the GCP Seminar

- Focus on areas of greatest risk
 - Legislative requirements, expectations, inspection findings re...
 - Protocol Compliance...**Sinéad**
 - Safety....**Donna**
 - Informed Consent.....**Sinéad**
 - IMP Management.....**Deirdre**
 - Training & Delegation....**Donna**
 - Q&A after each presentation. Other queries to compliance@imb.ie



IRISH MEDICINES BOARD

Agenda

- Aims of the GCP Seminar ✓
- Inspector Responsibilities ✓
- Overview of Legislation and Guidance ✓
- GCP Inspection References ✓
- Scheduling GCP Inspections ✓
- GCP Inspection Process ✓



IRISH MEDICINES BOARD

Agenda contd.

- Classification of Inspection Findings ✓
- Inspection Follow-up ✓
- GCP Inspection History ✓
- Summary of GCP Inspection outcomes
2007, 2008, 2009 ✓

- Aims of the GCP seminar ✓



IRISH MEDICINES BOARD

Thank you for your attention!



IRISH MEDICINES BOARD