



IRISH MEDICINES BOARD

Investigational Medicinal Product (IMP) Management

GCP Seminar Dublin, 27th January 2010

Deirdre O'Regan
GCP/ Pharmacovigilance Inspection
Manager

Objectives

- Investigator site staff responsibilities
 - Requirements
 - Deficiencies and Expectations
 - Inspections



IRISH MEDICINES BOARD

Requirements

- Note for Guidance on Good Clinical Practice: Consolidated Guideline (ICH Topic E6, Step 5) CPMP/ICH/135/95
- European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004 (S.I. No.190 of 2004)
- Medicinal Products (Control of Manufacture) Regulations 2007 and 2009 (S.I. No. 539 of 2007, S.I. No.4 of 2009)



IRISH MEDICINES BOARD

Requirements

- EU Guideline for GMP: Annex 13: Manufacturing of Investigational Medicinal Products (Directive 2003/94/EC)
- Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials (Volume 10)



IRISH MEDICINES BOARD

ICH GCP 4.1.2

- Requirement



➤ ICH GCP 4.1.2: *“The **investigator should be thoroughly familiar with the appropriate use** of the investigational product(s), as described in the protocol, in the current investigator’s brochure, in the product information and in other information sources provided by the sponsor.”*

- Deficiency

- Lack of awareness of the requirements

- Expectation

- Key documents available to the Investigator at the site
- Updated documents provided in a timely manner
- Evidence of IMP specific training (ICHGCP 4.2.4)
 - e.g. Investigator meeting, initiation visit, updates



IRISH MEDICINES BOARD

ICH GCP 4.6.1

- Requirement

- ICH GCP 4.6.1: *“**Responsibility** for the investigational product(s) **accountability** at the trial site(s) rests with the investigator/institution”*



- Deficiency

- Responsibility for IMP accountability not documented on the Delegation Log

- Expectation

- Responsibility for IMP accountability documented for the duration of the trial



IRISH MEDICINES BOARD

ICH GCP 4.6.2

- Requirement

- ICH GCP 4.6.2: *“Where allowed/required, the investigator/institution **may/should assign** some or all of the investigator//institution’s duties for investigational product(s) accountability at the trial site(s) to an appropriate **pharmacist** or another appropriate individual who is under the supervision of the investigator/institution.”*

- Deficiency

- No record of assignment of responsibility for IMP accountability to named Pharmacist(s)

- Expectation

- Documentation on the Delegation Log
- Record of trial specific training of Pharmacy staff



IRISH MEDICINES BOARD

ICH GCP 4.6.3

- Requirement

- ICH GCP 4.6.3 *“The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should **maintain records** of the product's **delivery to the trial site**, the **inventory at the site**, the **use by each subject**, and the **return to the sponsor or alternative disposition of unused product(s)**. These records **should include dates, quantities, batch/serial numbers, expiration dates** (if applicable), **and the unique code numbers assigned to the investigational product(s) and trial subjects**. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor”*



IRISH MEDICINES BOARD

ICH GCP 4.6.3 contd.



- Deficiency
 - Incomplete accountability records
 - IMP labels not fully completed by site staff
 - Drug accountability records for Subject ... were not adequately maintained
 - No record of the number of containers dispensed to Subject X or of the unique number of the IMP kit from which containers were dispensed
 - Subject Y did not return all containers dispensed at Visits 2 and 3. It was not possible to confirm that the subject complied with the dosing schedule between those visits



IRISH MEDICINES BOARD

ICH GCP 4.6.3 contd.



- Deficiency
 - Subject returned unused IMP as required but accountability records were not updated
 - During a tour of the pharmacy it was noted that Subject Y had returned one IMP bottle. Accountability records had not been updated to reflect this and were not, therefore, maintained in a timely manner
- Unused IMP was not accounted for and was not retained at site



IRISH MEDICINES BOARD

ICH GCP 4.6.3 contd



- Expectation

- Records of

- *delivery to the trial site (shipment and receipt dates)*
 - *inventory at the site*
 - *use by each subject*
 - *return to the site of unused IMP*
 - *return to the sponsor or alternative disposition of unused IMP*

- Records to include

- dates, quantities, batch/serial numbers, expiration dates and the unique code numbers assigned to the investigational product(s) and trial subjects



IRISH MEDICINES BOARD

ICH GCP 4.6.3 contd



- Expectation
 - **Every effort** should be made to obtain unused IMP and reconcile returned IMP
 - Investigators should maintain records to document that subjects were provided the doses specified by the protocol
 - **Timely** and **complete** accountability records



IRISH MEDICINES BOARD

ICH GCP 4.6.4



- Requirement

- ICH GCP 4.6.4: *“The investigational product(s) should be **stored as specified** by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirements.”*

- Deficiency

- No temperature monitoring records for the area where the IMP was stored from to....
- Temperature records were not signed and dated



IRISH MEDICINES BOARD

ICH GCP 4.6.4 contd.



- Deficiency

- Minimum and maximum temperatures were not recorded for either the fridge or the storage cupboard and, therefore, there was no evidence that the temperatures were within acceptable limits
- Temperature excursions were noted for the refrigerator between and No action was taken



IRISH MEDICINES BOARD

ICH GCP 4.6.4 contd.



- Deficiency
 - There was no evidence of calibration of thermometers used for monitoring the storage temperature of the IMP at site and no evidence of awareness of the requirement for calibration
 - IMP was not stored in a locked secure area, as required by the protocol
 - IMP was stored on an open shelf within the preparation room of the pharmacy
 - The fridge where the IMP was stored was located in a public place and was not locked



IRISH MEDICINES BOARD

ICH GCP 4.6.4 contd.



- Deficiency

- IMP was shipped on X date and receipt at site was logged several days/weeks later. There was no documentation of the conditions under which the IMP was stored in the interim. Temperature during shipment may have exceeded 2-8°C



IRISH MEDICINES BOARD

ICH GCP 4.6.4 contd.



- Expectation
 - IMPs shipped and **stored as specified** by the sponsor
 - Signed and dated records of the storage environmental conditions maintained
 - Evidence of calibration of temperature monitoring devices
 - Documentation and investigation of deviations
 - Evidence of corrective and preventive action in response to deviations



IRISH MEDICINES BOARD

ICH GCP 4.6.5



- Requirement
 - ICH GCP 4.6.5 *“The investigator should ensure that the investigational product(s) are **used only in accordance with the approved protocol.**”*
- Deficiency
 - Adequate procedures not in place
 - Training effectiveness questionable
 - Deviations not documented and investigated
- Expectation
 - Records to demonstrate compliance
 - CAPA



IRISH MEDICINES BOARD

ICH GCP 4.6.6



- Requirement
 - ICH GCP 4.6.6 *“The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.”*



IRISH MEDICINES BOARD

ICH GCP 4.6.6 contd.

• Deficiency



- Subject was non-compliant in taking study medication throughout the course of the trial
 - There was no evidence that the subject had been counselled regarding the need to comply
 - There was no record in the medical notes of the days on which medication was not taken or the reasons why medication was not taken
 - Non compliance of Subject X in taking study medication was not accurately documented in the case report form

- There was no documented evidence that subjects were reminded to return IMP at each visit



IRISH MEDICINES BOARD

ICH GCP 4.6.6 contd.

- Expectation

- Evidence in the subject notes that the correct use of the IMP was explained
- Evidence that site staff checked while the trial was ongoing that the subjects remembered /understood the requirements e.g. to return unused IMP
- Evidence that CAPA was taken when misunderstanding/non-compliance was evident



IRISH MEDICINES BOARD

ICH GCP 4.7



- Requirement

- ICH GCP 4.7 – Randomisation Procedures and Unblinding “*The investigator **should follow the trial’s randomisation procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g. accidental unblinding, unblinding due to a SAE) of the investigational product(s)***”

- Deficiency

- Subject unblinding not clearly documented in the source notes or reported to the sponsor



IRISH MEDICINES BOARD

ICH GCP 4.7 contd



- Expectation
 - Protect the blind
 - Maintain records of unblinding and timely reporting to sponsor
 - If accidental unblinding CAPA reports required
 - Training/re-training re. study blind and importance of maintenance of the blind



IRISH MEDICINES BOARD

ICH GCP 4.9.1



- Requirement

- ICH GCP 4.9.1 *“The investigator should ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports”*

- Deficiency

- IMP doses taken while subjects were at home were not recorded
- Accountability records were incomplete and it was not possible to assess subject compliance



IRISH MEDICINES BOARD

ICH GCP 4.9.1

- Expectation



- Records should include all data required by ICH GCP 4.6.3
- Records should be
 - Filed appropriately and securely
 - Completed accurately in a timely fashion
 - Signed and dated by responsible person



IRISH MEDICINES BOARD

Sponsor Responsibility

- Includes

- 5.14 Supplying and Handling Investigational Product(s)

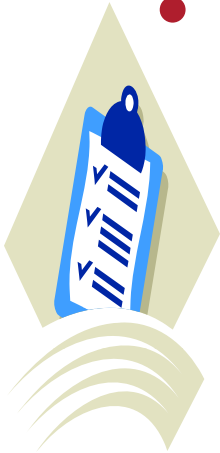
- 5.18.4 *Monitor's Responsibilities*

- (c) Verifying, for the investigational product(s)....



IRISH MEDICINES BOARD

Sponsor Responsibility



- Requirement

- *ICH GCP 5.14.3: “The sponsor should ensure that **written procedures** include instructions that the investigator should follow for the handling and storage..”*

- Deficiency

- The instruction in the CRF guideline did not facilitate accurate completion of IMP compliance data the CRF
- Missed doses were not documented in accordance with the CRF instructions. No queries were raised by the Sponsor regarding these omissions



IRISH MEDICINES BOARD

Sponsor Responsibility



- Requirement
 - *ICH GCP 5.18.4 (c) Monitor's Responsibilities*
- Deficiency
 - Drug accountability was not performed by the monitor during monitoring visits
 - There was no evidence that deficiencies in subject counselling and compliance were identified by the monitor
 - There was no evidence that the cold chain was maintained while the IMP was in transit and this was not queried by the monitor



IRISH MEDICINES BOARD

Sponsor Responsibility

- Requirement

- ICH GCP 5.14.4(c) *“The sponsor should maintain a **system for retrieving** investigational products and **documenting** this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim)”*



- Deficiency

- There was no procedure in place for retrieval of IMP in the event of a product recall
- Neither the Monitor nor the Site Staff were trained in the IMP recall procedure



IRISH MEDICINES BOARD

S.I. No.190 2004



- Requirement: *Good clinical practice and protection of clinical trial subjects,* Regulation 24
 - (3): IMP Free of charge (FOC)
 - (4): FOC does not apply to a non-commercial clinical trial that is conducted by an investigator-sponsor, who has no financial interest in the outcome of the trial except if products have been provided FOC



IRISH MEDICINES BOARD

S.I. 190 of 2004

- Requirement: *Labelling of Investigational Medicinal products. Regulation 43*
 - Particulars to appear on outer packaging of an IMP, or where there is no outer packaging, on the immediate packaging shall be:
 - Such as to ensure protection of the subject and traceability
 - To enable identification of the product and trial
 - To facilitate proper use of the IMP
 - In the English language
 - Labelling & re-labelling requirements in Annex 13



IRISH MEDICINES BOARD

Inspection

- Delivery of IMP
 - Were all approvals in place prior to shipment?
 - Was IMP delivered in a timely manner?
 - Shipping and receipt dates recorded?
 - Package correctly labelled, showing final destination and name of manufacturer /sponsor and required storage conditions?
 - Was condition upon receipt documented?
 - If necessary, was cold chain (2-8°C) maintained from shipment through to receipt? Documented?



IRISH MEDICINES BOARD

Inspection

- Storage of IMP
 - Controlled access to IMP from receipt to destruction?
 - Sufficient storage space?
 - Necessary segregation of stock?
 - Returns clearly identified and stored in separate area?



Inspection

- Storage equipment
 - Refrigerators
 - Regular servicing and related records?
 - If continuous temperature monitoring conducted, must be checked, signed off and filed in trial file
 - Procedures in place to handle temperatures excursions?
 - Back up generator?
 - Alarm system?
 - Procedure to handle trial supplies following excursions?



IRISH MEDICINES BOARD

Inspection

- Temperature Monitoring
 - Daily temperature monitoring
 - Signed and dated records of temperature
 - Thermometers must be a continuous monitoring device, e.g. max/min thermometer
 - Thermometers must be calibrated at least annually or replaced by calibrated thermometers
 - Consider temperature mapping



Inspection

- IMP Preparation
 - Procedures discussed with investigator/pharmacist and compared with protocol/instructions
 - Adequate facilities and equipment to prepare IMP?



IRISH MEDICINES BOARD

Inspection

- IMP Use
 - Check accountability records against:
 - Source data, i.e. subject chart, patient diary
 - CRF entries
 - Protocol requirements



IRISH MEDICINES BOARD

Inspection

- Destruction
 - Check that destruction **post-dated** verification by, or on behalf of, the sponsor of accountability records
 - Records should include authorisation of destruction by sponsor



IRISH MEDICINES BOARD

Inspection

- **Recalls**
 - Have a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim)
 - The investigator and monitor need to understand their obligations under the retrieval procedure (Annex 13)
 - The sponsor should ensure that the supplier of any comparator or other medication has a system for communicating to the sponsor the need to recall any product supplied.



IRISH MEDICINES BOARD

In summary....

- Requirements
- Deficiencies
- Expectations
- Inspections

With emphasis on site staff responsibilities



IRISH MEDICINES BOARD

Useful References

- Inspectors Q&As on European Medicines Agency websites
 - www.ema.europa.eu/inspections/GMPfaq.html
 - www.ema.europa.eu/inspections/GCPQaA.html



IRISH MEDICINES BOARD

Thank you for your attention
Questions?



IRISH MEDICINES BOARD