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Investigational Medicinal Product (IMP) Management

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Objectives

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



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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)



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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)



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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

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



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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



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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”*



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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



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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



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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



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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



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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



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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



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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



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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



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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



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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



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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.”*



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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



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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



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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



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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



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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



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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



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Sponsor Responsibility

- Includes

- 5.14 Supplying and Handling Investigational Product(s)

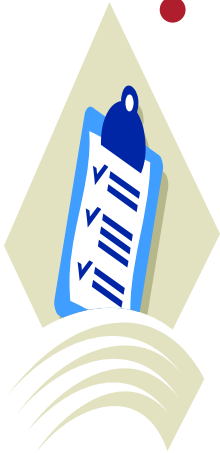
- 5.18.4 *Monitor's Responsibilities*

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



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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



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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



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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



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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



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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



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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?



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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?



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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?



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Inspection

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



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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



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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.



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In summary....

- Requirements
- Deficiencies
- Expectations
- Inspections

With emphasis on site staff responsibilities



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Useful References

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



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Thank you for your attention
Questions?



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