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Good Manufacturing Practice for
Investigational Medicinal Products

Tutor: Jo Burmester

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Agenda

- Refresher
  - Documents which apply
  - Definitions
- New version of Annexe 13
- Brexit latest
- Site Management for IMP

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The Laws

- Current EU Legislation and Guidance:
  - Eudralex vol 4
  - Annexe 13
  - Clinical Trials Regulation
- UK
  - Statutory Instrument 1031
  - Statutory Instrument 1928
- International
  - ICH GCP

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Definitions

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- True or False?

Definition of IMP also includes comparator	
QP stands for Qualification Protocol	
The Product Specification File contains exactly the same information as the Investigators Brochure	

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EU Clinical Trials Legislation

Option until Jan 23:
- Clinical Trials Directive
- GCP Directive
- GMP Directive

Future (From Jan 2022):
- Clinical Trials Regulation
- GMP Regulation

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EU CTR Application Timelines

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EU CTR:
- Adopted in 2014
- Applied from January 31st 2022

- **Jan 2022**
  - New Clinical Trials: Optional CTD or CTR
  - Transition of Ongoing Clinical Trials: Optional
- **Jan 2023**
  - New Clinical Trials: Required to follow CTR
  - Transition of Ongoing Clinical Trials: Optional
- **Jan 2025**
  - All clinical trials to follow EU CTR

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EU Clinical Trials Regulation

'Investigational medicinal product' means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial

'Auxiliary medicinal product' means a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product

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EU Clinical Trials Regulation

'Manufacturing' means total and partial manufacture, as well as the various processes of dividing up, packaging and labelling (including blinding)

'Auxiliary medicinal product' means a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product

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IMP Manufacture and Management

- Appropriate and proportionate
- Depends on regulatory status of IMP and type of trial
- Authorisation required except for these when done in hospital/health centre, by authorised staff and for use in same CT in same country:
  - Relabelling or repackaging
  - Prep of diagnostic radiopharmaceuticals
  - Preparation of medicinal products for direct administration to patients

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Labelling

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(a) information to identify contact persons or persons involved in the clinical trial;
(b) information to identify the clinical trial;
(c) information to identify the medicinal product;
(d) information related to the use of the medicinal product.

Detailed label info is in Annexe VI – same as Annexe 13 but have to identify products even for blinded trials

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For Unblinded Authorised IMP

- E.g. hospital stock
- Need to add to labelling:
  - Name of main contact
  - clinical trial reference code allowing identification of the clinical trial site, investigator, sponsor and subject
  - "For Clinical Trial Use only" or similar

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EU Guidance Documents

- GMP for IMPs
- AxMPs
- Risk Proportionate Approaches

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Eudralex Vol 4

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- Contents:
- Part I: Basic Requirements for Medicinal Products
  - Chapter 1 Quality Management
  - Chapter 2 Personnel
  - Chapter 3 Premises and Equipment
  - Chapter 4 Documentation
  - Chapter 5 Production
  - Chapter 6 Quality Control
  - Chapter 7 Contract Manufacture and Analysis
  - Chapter 8 Complaints and Product Recall
  - Chapter 9 Self Inspection
- Part II: Basic Requirements For Active Substances Used As Starting Materials
- 20 Annexes

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GMP for IMPs Guidance Updated Guideline

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- In chapter III of Eudralex Vol 10
- Appendix 13 to Eudralex Vol 4
- Remember the rest of Eudralex vol 4 also applies.
- New Version coming in with EU CT Regulation

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GMP for IMPs

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Production
Quality Control
Premises /Equipment
Batch Release
Labelling
Annexe 13
Free movement
Contract Manufacture
Documentation
Complaints
Personnel
Quality Management
Recalls/Returns
Shipping /Destruction

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Annexe 13

- Key Changes
  - New part in Section 2: The selection, qualification, approval and maintenance of suppliers of starting materials
  - PSF – added stability plans & reports, plus procedures for reference and retention samples

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Annexe 13 changes

- More detail on risk assessment for control of production and cross contamination risks
- Document retention
  - PSF At least 5 years, sponsor obligation of 25 years to be specified and agreed
  - Batch manufacturing records at least 5 years

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Annexe 13 changes

- Reference sample for comparator if changes made
- Blinding – expiry date to be the shortest one
- Repackaging exemption – in accordance with CT Reg – same clinical trial, same member state

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Annexe 13 changes

- Labelling – content is in CT Reg
- Relabelling (extending expiry date) carried out in separate area, line clearance at start and end

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Annexe 13 changes

- Sample retention
  - 2 years after end of clinical trial(s) (GMP Reg)
  - Not needed for unblinded authorised comparator
  - Samples retained in EU if possible

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New Guidance "Auxiliary Medicinal Products"

- Will replace IMPs and Non-IMPs guideline
- Can be found in Eudralex Vol 10 chapter III

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New Guidance AxMPs

- Key Changes
- Definition: “a medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product”

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AxMPs

- Con meds excluded
- Subject should not pay for AxMPs or equipment needed for administration
- Safety reporting for unlicensed AxMPs

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Risk Proportionate Approaches (New EU Regulation)

- Definition of Low-Interventional – do you know what it is?

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Low Interventional

- Evidence to support off label use could be:
  - evidence based treatment guidelines,
  - health technology assessment reports
  - clinical trial data published in scientific peer-reviewed journals
  - other appropriate evidence

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Low Interventional

- Examples of low interventional assessments:
  - measuring height and/or weight, questionnaires,
  - analysis of saliva, urine, stool samples, EEG and ECG measurements,
  - blood withdrawal through a pre-existent catheter or with minimal additional venepuncture.
- However any assessment which is much more frequent than normal can make the trial more interventional

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Risk Assessment

- Consider systems risks as well as trial risks
- Conduct Risk Assessment before protocol finalised
- Include relevant functions e.g.
  - data managers, statisticians, trial managers, pharmacovigilance personnel, monitors and/or auditors,
  - personnel who have more direct involvement with patients such as clinical experts,
  - investigators with an understanding of the therapeutic area and use of the proposed IMP, pharmacists, research nurses and laboratory experts.

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Risk Adaptations

These are areas where the CT Regulation allows risk adaptations for low interventional trials:

Table 2 Areas where risk adaptations can be applied

Risk Adaptations	Areas impacted	Section of the CT Regulation
1. Safety reporting	Safety profile of IMP Reliability of safety information	Article 41(2) Annex III(2.5, 21)
2. IMP Management	Traceability and accountability	Article 51(1)
3. Trial management	Monitoring	Article 48
4. Trial documentation	Content of the Trial Master File (TMF)	Article 57

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Risk Adaptations

- IMP
- Traceability and Accountability
  - Documentation in line with source and nature of use in the trial
  - Can use hospital stock for low interventional trials
  - Traceability rather than full accountability for low interventional trials
- Monitoring of storage conditions justified by risk assessment

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IMP and Brexit

- QP certification from other EU countries will still be recognized – oversight by UK QP
- IMPs can be sent direct to investigational sites
- Import license required
- Will need EU QP release after export from UK

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Importing IMP Post Brexit

- QP oversight required to confirm appropriate QP Release
- Documentation of oversight
- Further information and guidance on MHRA website

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The Future in the UK

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- MHRA have consulted on revised legislation
- First new legislation likely to come out later this year
- Many aspects of EU CTR and ICH E6(R3) will be implemented

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MHRA priorities for new legislation

- Patient focus
  - Involvement in research planning
  - Transparency
  - Diversity
- Streamlined processes
  - Combined Review
- Risk proportionality
  - Risk adapted approaches
  - Notification scheme for low interventional
- Agile
  - Flexibility – able to adapt to innovation
- International
  - In line with international standards

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Site management of IMP

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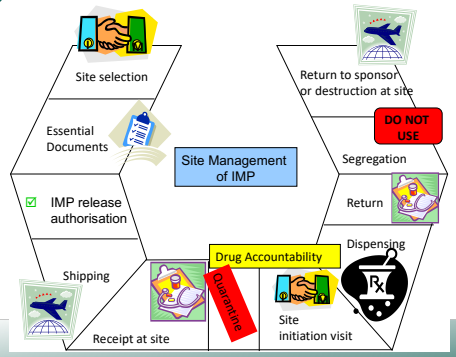

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Site Management of IMP

Poll

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Site Management of IMP

- Personnel
- Premises
- Processes

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Site Management of IMP

- Personnel
  - Pharmacist, Investigator, Nurses, Subjects
  - Trained in study procedures
  - Trained in drug storage, dispensing and accountability

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Site Management of IMP

- Premises
  - Storage
  - Equipment
    - Calibration
    - Maintenance
  - Quality control
  - Documentation

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Site Management of IMP

- Processes
  - Storage
    - Temperature
    - Light
    - Humidity
  - Access
    - Locked
    - Limited access
  - Status
    - Quarantine
    - Returns – need to be in separate location and clearly marked

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Site Management of IMP

- Processes
  - Randomisation and blinding
    - Train staff and check randomisation
    - Check blinding at every visit
  - Dispensing
    - Prescription process
    - How does it get from pharmacy to patient?
    - What QC checks for dispensing?
  - Accountability
    - Every tablet, vial, blister
    - Keep up to date

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Site management of IMP

- Processes
  - Returns
    - Kept separate so not used for other patients
  - Disposal
    - Returned to sponsor
    - Destroyed at site with written sponsor approval
    - Documentation

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