IRISH MEDICINES BOARD

Computerised Systems

Inspection Expectations

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Presentation Contents

IRISH MEDICINES BOARD

- Brief Introduction to the IMB
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Brief Introduction to the IMB

Mission Statement

IRISH MEDICINES BOARD

‘To protect and enhance public and animal health through the regulation of medicines, medical devices and health care products’

Irish Medicines Board -*Summary*

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- Competent Authority in Ireland for medicinal products for human use
- medicinal products for veterinary use
- medical devices
- blood and tissues & cells
- Cosmetics
- Organs

- Licensing and Inspection of Controlled Drugs in conjunction with Department of Health & Children

IMB –Some Facts and Figures

IRISH MEDICINES BOARD

- Formerly National Drugs Advisory Board (NDAB)
- Established under IMB Act 1995 (No. 29 of 1995)
- Region of 260 staff members
- Assess & monitor over
  - *6,700 Human Medicines*
  - *1,200 Veterinary Medicines*
  - *500,000 Medical Devices* on the Irish market

Regulatory References

Regulatory References

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- EU GMP Annex 11 (2011)
  - Free
  - http://ec.europa.eu/health/files/eudralex/vol-4/annex11_01-2011_en.pdf
- EMA Questions and Answers on Annex 11
  - Free
  - http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/gmp_q_a.jsp&mid=WC0b01ac058006e06c#section8
- PIC/S PI 011/3 (2007)
  - Free
  - http://www.picscheme.org/pdf/27_pi-011-3-recommendation-on-computerised-systems.pdf

Changes to Annex 11

Annex 11: Changes

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- Principle:
  - Computerised System:
    - Software and Hardware components which together fulfill certain functionalities
    - No resultant decrease in product quality, process control or quality assurance
- This is what is to be achieved

Annex 11: Changes

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- Scope has increased

- Now includes everything from…
  - Electronic Batch Record Systems
  - Manufacturing Control Systems
  - Building Management Systems
  - Lab Management Systems
  - Document Management Systems
  - Training Management Systems

Annex 11: Scope

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- To…
  - Small devices e.g. Temperature loggers
  - IT Incident Tracking Systems (for GMP systems)
  - Electronic Request Systems (e.g. user account requests)

- In other words….
  - All systems engaged in GMP activities!
- Applications: Validated
- Infrastructure: Qualified

Annex 11: Changes

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- Annex 11 is written in three sections
  - General
  - Project Phase
  - Operational Phase

Annex 11: General

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- Risk Management
  - Required throughout the lifecycle
- Roles and Responsibilities
  - Process Owner:
    - Responsible for the Business Process
  - System Owner:
    - (Typically) Responsible for
      - Availability of system
      - Maintenance of system
      - Security of the data on the system

Annex 11: General

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- Personnel
  - …appropriate…level of access and defined responsibilities to carry out assigned duties
- Have they access to
  - enough?
  - too much?
- How is this maintained with corporate/multisite systems?

Annex 11: General

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- Something to consider...
  - Do sister site personnel have access to your elements of a multisite system which is beyond their responsibility and duty?
  - If so, are they trained (within your QMS) and authorised to access your elements?

Annex 11: General

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- Suppliers and Service Providers
  - Who is supplying the system?
  - Who is maintaining it?
  - Agreements as per Chapter 7
    - Even with internal IT departments
  - Assessment of supplier/service providers
    - Appropriate Standards used?
      - e.g. ISO 12207, ISO 25010 as appropriate
    - Audit required? – justify decision

Annex 11: Project Phase

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- Validation of Systems
- Annex 11 Assessments
- Considerations for Validation

Project Phase: Validation

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- Up to date listing of all relevant systems and GMP functionality

- Critical Systems
  - System description data flows, interfaces with other systems, processes.
  - Software/Hardware pre-requisites
  - Security measures

- User Requirements:
  - Based on risk assessment and GMP impact
  - Traceable throughout the lifecycle

Project Phase: Validation

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- Generally follow the lifecycle of equipment validation: IQ, OQ, PQ with quality gates at the appropriate points.

- Level of validation depends on the criticality of the system
  - This should be justified

Project Phase: Validation

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- What do you test?
  - Process (parameter) limits
    - Values
    - Logic
    - User Accounts
    - Configuration
    - Multiple connections
    - Simultaneous requests

Project Phase: Validation

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- Data limits
  - Include negative testing (from risk assessment)
- Error handling
  - System recovery mid transaction?
  - Database corruption
  - Hardware buffers etc
- Data Transfer
  - Checks that data are not altered in value and/or meaning
  - Level of checking should be statistically sound

Annex 11: Assessment

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- Current Annex 11 effective 30th June 2011
- It is now 2013
  - Expectation that company's have assessed their systems against the updated Annex.
- What should this assessment cover?

Annex 11: Assessment

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- Gap analysis of the quality management system elements relating to computerised systems:
  - Policies and SOPs
  - Agreements
  - Listing of Systems
  - Categorisation of Systems
    - (critical/non-critical)

- Assessment of Legacy Systems

Annex 11: Legacy Systems

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- For each Legacy System:
  - Define the user requirements
  - Perform a gap analysis to determine the validation effort for retrospective validation.
  - Verify user requirements

Considerations for validation

Small Device Validation

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- Usually widely used off-the-shelf pieces of equipment
  - Temperature logger
- Development life-cycle is mainly controlled by the vendor.
- A vendor assessment is required

Small Device Validation

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- Generate Requirements Definition for the intended use including process limitations.
  - Is data are stored or transferred to another system.
  - Parameter data influencing the device's behaviour should not be altered without suitable permission

- Risk assessment
  - consideration for the intended use and patient risk

Small Device Validation

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- Documentation from the vendor
  - methodology used and the calculation algorithm (if applicable).
  - Vendor certificate or equivalent detailing the testing performed by the vendor
  - Calibration certificate (if applicable)

- Develop Validation plan according to the risk-assessment results

- Verification testing (PQ-phase).

“Third Party” Validation

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- Qualification/Validation performed by a ‘Vendor’
- Subject to Chapter 7: Outsourced Activities
- Site must ensure their user requirements not the ‘Vendors’ are achieved.
- Validation is the responsibility of the regulated user...
- What about Multisite/Corporate Systems?

Corporate/Multisite Systems

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- Some examples:
  - ERP System
  - Deviation Management System
- Validation plan/overview for the approach taken
- Typically some ‘Corporate’ core validation
  - Plan, URS, FDS, IQ, OQ etc
- Site should assess the corporate validation
  - include Site Infrastructure
  - Must meet the requirements of Annex 11

Corporate/Multisite Systems

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- Typically ‘Site’ performs activities to mitigate the risks identified
  - Some Infrastructure Qualification
  - Some software and configuration elements:
    - Mini URS, Mini FDS/Config Spec, Mini IQ, Mini OQ, PQ etc.

- All documentation may be subject to inspection
  - Includes ‘Corporate’ core validation and associated assessments, agreements etc

Corporate/Multisite Systems

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- Remember:
  - ‘Corporate’ HQ typically not involved in manufacturing and are therefore not usually regulated
  - Validation is the responsibility of the regulated user...

What about Spreadsheets?

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- Assess the situation…
  - Do you need to consider the package (Excel) or the spreadsheet?
    - Assess requirement of each spreadsheet generated.

- Validation is required for spreadsheets that contain custom code.
  - E.g. Visual Basic

What about Spreadsheets?

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- Formulas (any algorithms) should be verified
  - ‘Template’ and ‘Record’ subject to requirements of Chapter 4

- Data integrity should be ensured.
  - Can formulas be accidentally overwritten?
  - Will input of an inappropriate data type be accepted?
    - No input or error message?
  - 'boundary checks’

Some other things to consider…

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- Where certain activities are outsourced by a manufacturer and computerised systems are used:
- The validation of such hardware and software should be maintained.
  - e.g. Kaye Validators etc
- Validation is the responsibility of the regulated user...

Annex 11: Operational Phase

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- Data
- Accuracy Checks
- Data Storage
- Printouts
- Audit Trails
- Change and Configuration Management

- Periodic Evaluation
- Security
- Incident Management
- Electronic Signature
- Batch Release
- Business Continuity
- Archiving

Operational Phase: Data

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- How does the system interface with other systems?
  - Native to the software?
  - Middleware?
  - Custom code?
  - E.g. EBR with Balances, CDS data migration to LIMS

Operational Phase: Data

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- Data security includes:
  - Data Integrity
  - Reliability
  - Availability of data.

- During validation of a database or inclusive system consider:
  - procedures and mechanisms to ensure data security, the meaning and logical arrangement of data
  - load-testing, incorporating future database growth
  - precautions for end of life-cycle data migration

Operational Phase: Accuracy Checks

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- How accurate is the data?
  - Electronic Verification e.g. against a database or other system
  - Manual verification of entries e.g. manually on to a calculation spreadsheet
  - The consequence of bad data should be known and assessed.

Operational Phase: Data Storage

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- How is it stored?
- Where is it stored?
  - Who has access?
  - Who should have access?
- Is Data integrity maintained?

Operational Phase: Printouts

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- Ensure that clear printouts of data can be obtained.
  - E.g. calibration schedules.

- Records supporting batch release should indicate if any data has been corrected.

Operational Phase: Audit Trails

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- Audit Trails must be
  - convertible to a ‘generally intelligible form’
  - regularly reviewed

- If system has no functionality showing changes to data since original entry
  - printout of the related audit trail report must be generated and linked manually to the record supporting batch release

Change and Config. Management

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- Remember, the system is validated!
- Changes to a part of the system may pose a risk due to interdependencies.
- Change management system must be used.
  - Record, assess, approve and document change
- Separate electronic system used for IT issues/changes?
    - …a GMP system in its own right?

Operational Phase: Periodic Evaluation

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- Periodic Evaluation frequency must be justified.
  - Criticality of system
  - Complexity of system
- Consider it like other periodic evaluations
  - e.g. Water System, Env Monitoring etc
- Some things to consider in the evaluation:
  - Current functionality
    - (any changes? Does it still meet user requirements?)
  - Deviations or Incidents
  - Problems

Operational Phase: Periodic Evaluation

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- Some more things to consider in the evaluation
  - Upgrade history
  - Performance
  - Reliability
  - Security
  - Validation Status Reports

Operational Phase: Security

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- User Access Levels
  - Definition of levels
- Management of access control
- Record of access within software
- Extent depends on criticality of system

Op. Phase: Incident Management

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- All incidents should be reported and assessed.

- What is an incident?
  - System Failures
  - Data Errors
  - Any unplanned issue affecting product quality or data integrity.

- Root cause of a critical incident should be identified and CAPAs implemented.

Op. Phase: Electronic Signatures

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- E-Signature must have the same impact as a hand written signature
  - Within the boundaries of the company
- If an e-record is from a third party how do you know that it meets the above?
  - If used, then they are a GMP system and should be validated as such
  - how have you verified this? - Supplier Qualification?
- Permanently linked to the record
  - Does your system rebuild the signed document or is the signature embedded within the document?
  - Has it been verified?
- Time and date stamped

Op. Phase: Batch Release

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- Only the QP certifies the batch
  - Captured by e-signature

- EBR Exception Reports considerations
  - Personnel review only exceptions
  - Risk Assessment
  - Assumption that all EBR modules correct
    - Critical times managed within EBR?
    - Indirect information correct?

Op. Phase: Business Continuity

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- What happens if the system breaks down?
- Manual or Alternative system?
- Risk Assessment for bringing them up
- Manual/Alternative systems should be tested in their own right

Op. Phase: Archiving

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- Is data verified?
- What is media used and what is its expiration criteria?
- Is data still retrievable when changes are made to the system?
- Storage requirements of electronic data and documents the same as paper documents.
- Ensure electronic signatures applied are valid for the entire storage period for the documents.

Sample Deficiencies

Sample Deficiencies: General 1/2

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- A listing of GMP computerised systems was not maintained.
- The software utilised to control [equipment] had not been categorised.
- Not all critical GxP systems were present. For example the [Equipment] Program and Review software.
- The Virtual Private Network software had not been subject to GxP assessment or qualification as appropriate.

Sample Deficiencies: General 2/2

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- The [business continuity process] was not available for use as documented in [a deviation]. The associated investigation did not assess why the contingency procedure and process had failed.

- The third party audit performed of the software supplier was considered deficient in that the memo describing the qualification or impartiality of the auditors was not physically signed.

- There was no system description defined despite the system being ‘live’.

Sample Deficiencies: User Accounts 1/2

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- It was permitted for [CDS] administrators who had audit trail access to analyse samples.

- It was possible for administrators to verify their own test result recording in ERP. There were no procedural restrictions around this and was hence considered to increase the overall risk of the associated testing processes.

- The ‘system owner access level’ was not described.

Sample Deficiencies: User Accounts 2/2

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- The removal of test accounts had not been considered by the company prior to the system going ‘live’.

- [ERP] access configurations for the job roles within the site was not adequately defined in that there was no documented correlation of local access levels to the user access elements as defined by the Global [ERP] group.

- System authorisation concepts were not always considered in that Users could be administrators with full system access and also have batch manufacturing responsibilities.

Sample Deficiencies: Audit Trail

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- Audit trail comments on [the CDS] were not always sufficiently detailed. For example, a number of changes were observed to have been made to the integration method utilised on [a test] on [a date] and these had a comment of ‘save’ documented.

Sample Deficiencies: Qualification 1/2

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- The qualification of the ERP system was considered deficient in that:
  - The independent code review was not available for review during the inspection.
  - The actual observed results were not always documented within the qualification records
  - The procedure for electronic signatures data transfer to the ERP system was not described in a procedure and was not qualified.
  - There was no assessment of ERP database integrity.

Sample Deficiencies: Qualification 2/2

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- The decision not to test requirement [Electronic Signatures] documented in [Rationale] was not considered to be justified in that the referenced documents disclaimer stated that the information should not be relied upon.

Sample Deficiencies: Assessments

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- The periodic assessment of computerised systems had not been completed for all equipment. For example, [computerised system] was installed [a long time ago] and at the time of the inspection had not been reassessed.

- The assessment of GxP systems against the requirements of the revised Annex 11 which came into effect 30th June 2011 had not been completed.

Sample Deficiencies: Archiving

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- In relation to the back up and restoration of data
  - There was no process for logging of media used to back up the server systems.
  - The maximum number of uses for the magnetic tapes was not defined or the number of uses controlled.
  - All backup activities on the site were not procedurised. For example back up of the [Program] data from [Equipment] and back up of certain [Equipment] PLC code was performed on an ad-hoc basis using HDDs which were not stored in an appropriate location.

In Summary…

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- Understand the system and its interactions
- Risk Assess the system
- Software should be validated and maintained
- Infrastructure should be qualified and maintained
- Data Integrity should be assured
- E-Signatures should be permanently linked
- Issues should be appropriately investigated and resolved

- There should be no resultant decrease in product quality, process control or quality assurance

Questions

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Thank You for Listening

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