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Regulatory Compliance Inspections at MAH Offices: *Implications for Manufacturers*

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What are Regulatory Compliance Inspections?

- Inspections that are carried out at the offices of marketing authorisation holders or their representatives in Ireland by the IMB
  - 3-5 Inspections per year since 2007
- Two-fold purpose:
  - To determine the level of compliance of MAH activities with the legal requirements for the marketing and advertising of medicinal products
  - To promote compliance and good practice - by increasing the focus on MAHs
- These are risk-based inspections – companies are selected using risk considerations
  - Past Compliance Issues
  - Range and criticality of products and extent of regulated activities
    - Large product range, essential products, extent of advertising activities
    - High risk products - for which accurate product information and medical information are essential
  - Complexity of the activities and arrangements in place
    - e.g. recent merger activity

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Possible triggers for inspection

Certain factors may determine which MAH offices will be inspected:

- Past compliance history of the company
  - e.g. Quality Defect & Recall profile, poor responses to regulatory requests, etc

- Suspected or confirmed GMP or MA non-compliance issues, e.g.
  - Adverse market surveillance findings
    - Non-compliant packs identified on the market
    - Analytical methods not updated post-variation approval
    - Shelf life not changed following variation to increase/reduce shelf life
  - Changes implemented prior to variation approval
  - No evaluation by MAH of results of Product Quality Reviews
  - Failure to make available correct PIL in a format suitable for the blind or partially sighted (Art 56a of Dir 2001/83/EC, as amended)
  - Failure to fully comply with Recall requests made by Competent Authority
  - Suspected non-compliant SPCs or PILs being provided by the MAH
  - New information affecting benefit/risk balance not reported to CA

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Why are Regulatory Compliance Inspections being performed?

Several reasons why we decided to look at MAH activities & controls via Inspection

Reason 1:

- Widespread MA non-compliance issues identified in Ireland in 2004-2006, and these continue to occur (but to a lesser extent)
  - e.g. failure to implement variations
  - e.g. using active substances or manufacturing processes that are not authorised

- These issues indicated the serious consequences that can result when failures in regulatory activities and regulatory/manufacturing interfaces occur
  - e.g. cessation of QP release and supply of products for several months
  - e.g. global product shortages

- These inspections are designed to get companies to focus on these areas, to ensure that quality systems are robust, and to prevent similar non-compliances occurring
  - IMB is seeing evidence that this goal is being achieved
  - e.g. increased focus on tracking artwork variations, training, etc.

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Why are Regulatory Compliance Inspections being performed?

Reason 2

- The IMB 2005 decision on how the Braille and the PIL-related provisions of Article 56a are to be regulated meant that there was a need to check compliance at MAHs against the Braille declarations submitted to the IMB by MAH companies
  - This inspection programme is designed to do this

Reason 3

- Non-compliant advertising activities may affect the safe prescribing and use of medicines… these activities can present risks to patients
  - Advertising activities are important to assess from a compliance perspective
  - MAH inspections provide an avenue to inspect advertising activities and the related controls at companies

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What Areas are inspected in this programme?

The areas inspected are divided into two main operational parts:

- Inspection of the controls in place for assuring Regulatory Compliance
- Inspection of the Quality Management System supporting the above controls and their related activities

  - See following slides

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Regulatory compliance…

- Regulatory Changes & Commitments:
  - How are these communicated to manufacturers, and how are changes implemented?
  - How are these communicated to internal staff, such as Medical Information and Sales & Marketing staff, and how are these communications used?
  - How adequate are procedures & technical agreements with manufacturers?

- Product Quality Reviews – is the MAH involved in PQRs?
  - How is compliance with Chapter 1 of GMP Guide achieved?

- Registered Product Information: how is this managed and used by the MAH company?
  - Can companies retrieve what is currently registered?
  - How is superseded registration information handled?

- SPCs & PILs: When these are provided by MAHs to HCPs, patients, websites and company sales representatives, how are these controlled and kept up-to-date?
  - How do companies manage & update SPCs on www.medicines.ie?
  - How are package leaflet user tests managed? Contracted out?

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Regulatory compliance…

- Quality Defects & other new information:
  - How is information that suggests a quality problem with a product managed & reported?
  - How are complaints logged and handled?
  - How are stability OOS results handled?
  - Are quality complaints differentiated from ADR reports?

- Product Recalls
  - How have these been managed by the MAH to date?
  - Have the agreed recall actions actually been complied with?
  - Are procedures in place to enable urgent recalls to be executed in a timely manner?

- OCABR
  - Is the supply of vaccines, blood & plasma products compliant with the Official Control Authority Batch Release requirements?
  - Is the MAH-nominated wholesaler aware of the OCABR arrangements?

- Braille – how are the provisions of Article 56a of Dir 2001/83/EC complied with?

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Regulatory compliance…

- Advertising programmes:
  - How are advertising programmes and materials approved, run and controlled?
    - Adequate medical oversight?
    - Are all promotional activities controlled as advertising activities?
  - Do advertisements comply with the 2007 Irish advertising regs?
    - In line with the SPC?
    - Objective & not misleading?
    - Absence of prohibited information, (such as by suggesting that the safety or efficacy of the product is due to the fact that it is *natural)*
    - Do advertisements promote the rational use of the product?
    - Do they contain all of the information which they must contain, e.g. information necessary for correct use?
  - Competency of Sales & Marketing Staff
    - e.g. Do Sales Reps have sufficient scientific knowledge to enable them to provide information on the product which is precise, complete and in line with the SPC?

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Regulatory compliance…

- Advertising programmes cont'd:
  - Free Medical Samples:
    - Are controls and records adequate?
    - Adequate storage and security arrangements in place?
  - Inducements & Hospitality:
    - What arrangements and controls are in place?
    - Inexpensive & relevant to the practice of medicine or pharmacy?
  - Promotional Aids:
    - Inexpensive, non-monetary, and relevant to the practice of medicine or pharmacy?
  - Sponsorship Activities:
    - What does the company sponsor, if anything? Cost and purpose?
    - Relevant to the practice of medicine or pharmacy?

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Regulatory compliance…

- Medical Information
  - What qualifications and training do Medical Information staff have?
    - Are there sufficient resources in place for the volume of queries received?
  - Where do Medical Info staff get their product information from?
    - Where do they access SPCs?
    - If pre-defined answers are used, how are these approved and kept up-to-date?
  - What records are kept of the queries and of the responses?
  - If a Medical Information service is provided for products marketed by other companies:
    - Who is responsible for ensuring that information sources contain the correct information?

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Quality Systems…

- What kind of QMS is in place, if any, at the MAH company?
  - GMP-based? ISO-based? ICH Q10-based? Other?
  - Externally assessed / accredited?

- What QMS resources are in place?
  - How is Quality represented at Senior Management level?
  - Is there a Quality Manager in place?
  - What QA resources support the QMS?
  - Do these staff have other duties, such as pharmacovigilance?

- Does the QMS extend to all regulated activities of the MAH, or just to selected areas?
  - Advertising?
  - Medical Information?
  - Brand Manager and Sales Rep training programme?

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Quality Systems…

- Are key elements of a QMS in place and are these operating effectively?
  - Documented job descriptions
  - Staff induction and on-going training programmes
    - Who provides training? Effectiveness of training?
  - Control of Registered Documentation – dossiers, specifications, SPCs, PILs, etc
  - Change Control for changes that may impact MA compliance and/or patient/animal safety
  - Deviation investigation & management
  - Complaint/Quality Defect investigation & management
  - Management Review / Self-inspection – how is compliance with the QMS monitored?
  - Risk-based validation or verification of critical systems
  - Contracts/ Tech Agreements with other parties, such as…
    - Manufacturers
    - Primary Wholesaler
    - Contracted sales force
    - NCBI, RNIB for Braille PILs, etc.

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General Findings & Deficiencies to date…

Some positive findings have been observed to date:

- High emphasis on continual improvement seen in some companies inspected, especially in the areas of:
  - Quality Management generally - to ensure that all areas controlled via the QMS
  - Training Activities – especially in the assessment of training effectiveness
  - Advertising programmes – increasing level of Regulatory & QA oversight

- Some companies do compliance checks on batches of products before their placement onto the market

- High level of expertise seen within the Regulatory functions in some cases
  - Evidence of involvement in Irish and global regulatory discussions, initiatives and regulatory developmental work

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General Findings & Deficiencies to date…

But deficiencies have been identified across many different areas of activity

- No Critical deficiencies identified, but several Majors & Others identified
  - The non-compliance issues in some cases led to the marketing and advertising of non-compliant medicinal products, e.g. with incorrect or out-of-date product information

- Many of the same non-compliance issues and problems observed at several companies
  - *Failure to track and check the implementation of CMC variations*
  - *Inadequate QA resources for the range of Marketing Authorisations held*
  - *Failure to comply with the PQR requirements of Ch. 1 of EC Guide to GMP*
  - *Failure to train Sales Representatives adequately*

- During several IMB Regulatory Compliance Inspections, QPs at manufacturing sites have been called to participate in the inspection
  - Increasing trend!
  - **Will you be called to participate in an MAH Inspection soon???**

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Common Deficiency Themes…

- Multiple and complex systems in place for the storage of registered information
  - MA Dossiers, CTD files, Product Specifications, SPCs, Artwork, etc.
  - Often, no clear procedures describing the storage and retrieval of such information

- Inadequate controls in place for the tracking of variations and for verifying their implementation
  - *Especially for non-artwork related variations*
  - Communication systems with manufacturing sites often an issue

- Inadequate controls in place for the management of regulatory commitments
  - Stability studies, process validation studies, etc. arising out of MA Renewals
  - High reliance on personal memory in some cases

- Inadequate controls in place for the management of electronic SPCs
  - Procedures for keeping SPC files up to date often lacking sufficient detail
  - Different levels of control sometimes seen for different types of documents, e.g. electronic SPCs vs. printed SPCs

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Common Deficiency Themes…

- Inadequate controls in place for the internal communication of important SPC changes
  - Many instances of this seen with safety-related changes
  - Sometimes, Medical Information staff and Sales & Marketing staff not informed

- Computer systems were often relied upon for assuring regulatory compliance of the products being marketed…
  - But often no verification of validation testing of critical functionalities carried out

- Sales and marketing staff often had not been trained on the contents of the Irish 2007 Advertising Regulations
  - Some promotional activities were not controlled as advertisements
  - Sometimes Sales & Marketing staff had no knowledge of key provisions in the Advertising Regulations
  - The level of knowledge of some Sales Representatives on key aspects of SPCs for products they were promoting was sometimes deficient

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Common Deficiency Themes…

- Quality Management Systems were often very complex in structure
  - Relatively convoluted arrangements governing how Quality Management activities operated at a practical level
  - Key responsibilities were often not documented
  - Staff reporting lines are sometimes very unclear

- Some regulated activities were not controlled via the company QMS
  - e.g. Advertising activities
  - e.g. Certain training activities

- Key elements of a QMS deficient or significantly lacking
  - Self inspection
  - Change Control
  - Training
  - Deviations Management
  - Documentation Management
  - Arrangements with important external parties

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Is any of this relevant to you….???

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MAH Activities & Manufacturers

How well do your know your MAH partner and its activities???

- Do you know the nature of their QMS and how well it operates? Evidence???
- Would you be concerned if your MAH company was not managing its MA documentation well and could not retrieve exactly what is currently registered?
- What would you do if you learned that an approval of a variation to tighten an impurity specification was never communicated to your site?
  - Where would you focus CAPA activities?
- How would you react if IMB performed market surveillance on a product your QP released and found the Package Leaflet was missing key safety-related information
  - e.g. WRT suicide-related warnings in an SSRI product?
    - Where would you focus CAPAs?
    - Whose responsibility is it to ensure the leaflet was up-to-date?

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MAH Activities & Manufacturers

How well do your know your MAH partner and its activities???

- What role does your MAH office have in supporting your site's batch release activities?
  - Is this role understood at a practical level within your company???

- How much do you rely, knowingly or unknowingly, on your MAH office to ensure the batches your site releases are MA-compliant?

  - What has your site done to ensure that this reliance is well founded?

    - A: We put a Technical Agreement in place with the MAH office
    - B: We rely on our Corporate Quality Group to oversee MAH activities
    - C: We routinely audit the activities of the MAH office and its QMS
    - D: We audited them once and they were okay
    - E: Not sure

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3 Recommendations for Consideration

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Recommendation 1

Work to understand how much reliance your site places in the activities of MAH offices, and focus your resources accordingly!

- Gain a working understanding of the procedures in place at MAH offices for:
  - Managing MA documentation and keeping it up-to-date
  - Documenting and communicating the outcome of variation and renewal applications
  - Communicating post-approval regulatory commitments to you
  - Tracking the implementation of variations and regulatory commitments
  - Compiling abbreviated versions of MAs that QPs may certify batches against
  - Responding to requests from Competent Authorities to vary MAs (e.g. PLs)
- Know how many MAH offices there are and how their QMSs may differ
- Understand the role, if any, of Corporate Quality in overseeing the MAH offices
- Understand the role, if any, of Corporate Regulatory Groups in managing variations and post-approval commitments

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Recommendation 2

Put systems in place to ensure that this reliance is well-founded

- Technical Agreements alone are not sufficient!
- Inter-company teams and robust communication systems are vital
- Audits of the activities and QMS of the MAH are important:
  - *Focus on what the MAH actually does to support the compliance status of your products*
  - *Ensure the interfaces between your site and the MAH office are audited*
  - *If there is a third-party involved (e.g. Global CMC group), ensure that their roles and responsibilities are documented and audited too!*

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Recommendation 3

Identify *Highly Complex & Tightly Coupled processes* and manage the related risks

- The systems that are needed to ensure that batches of medicinal products comply with their MA are becoming increasingly complex and 'coupled', as a result of:
  - Globalised supply chains & increased use of outsourcing
  - Just-in-time manufacturing, low inventory management, site rationalisation
  - Company mergers - resulting in multiple regulatory systems and repositories of information

Complex systems are systems with:

- Multiple parties involved in work processes, with multiple steps & multiple sign-offs
- Design features, such as branching and feedback loops, in work processes
- Unplanned or unexpected sequences which are not visible or not immediately comprehensible
- Opportunities for failures to jump across subsystem boundaries

Tightly-coupled systems are described as having:

- Time dependent processes that cannot wait
- Rigidly ordered processes, as in Step B must follow A
- Only one path with a successful outcome

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Recommendation 3 cont'd

- Things can go wrong in complex and coupled systems that can be completely unforeseen and difficult to model!!
  - Normal Accident Theory!
  - See Greenfield M.A., "Normal Accident Theory - the Changing Face of NASA and Aerospace, NASA Office of Safety and Mission Assurance, November 17th, 1998
- The interfaces between MAH offices, manufacturers and regulators can involve highly complex and tightly coupled processes
  - Think of what it takes to ensure compliance with an artwork variation involving 27 Member State markets, multiple language variants and varying approval times!

It is important, therefore, that manufactures and QPs understand which processes involving MAH offices are tightly coupled and are highly complex

•This allows you to ensure that those processes are well documented, understood, resourced and monitored!
•The concepts of ICH Q10 are useful here - Process Performance & Product Quality Monitoring, Knowledge Management
•See Journal of GXP Compliance, Vol. 12 No. 4, Summer 2008 for further discussion

Questions / Discussion?

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