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# ***Self-Inspection and its potential benefits via ICH Q9 & Q10***

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# Topics for today...

- Why talk about Self-inspection today?
- What the EU GMPs currently require in this area
- The role of Self-inspection in averting GMP Deficiencies and Potential Recall Issues
  - The benefits of critically reviewing your Self-inspection programme
  - Some practical things to look at
  - Understanding Complexity & Coupling in Manufacturing Arrangements & Processes
    - Working towards a more risk-based Self-inspection programme
- A Changing Regulatory Environment - ICH Q8, Q9 & Q10
  - What role might Self-inspection play?



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# Why Talk about Self-Inspection?

- **Self-Inspection is a well established part of the EU GMPs**
  - A full Chapter in Part I of the EU GMP Guide (Ch. 9)
  - Specific section (2.4) in Part II (for active substance manufacturing)
  - Little change in this area over several years
    - No plans to review this guidance at this time
- **Companies are all running self-inspection programmes**
  - Regulatory Inspectors verify this but do not normally review self-inspection reports
  - Self-inspection, for some, is an intimate, private thing that companies do and that regulators should respect & not interfere with
  - There have been few Major or Critical Deficiencies directly involving self-inspection activities in recent years
- **So what is the problem?**
  - What is there to talk about at a day like this?



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# Three reasons...

Deficiencies identified in GMP Inspections and potential recall issues investigated in Market Compliance activities are often not identified via self-inspection

- This is sometimes surprising to Inspectors, especially for Major and Critical Deficiencies and for many potential recall issues
- How can this be addressed while still keeping the spirit and the non-interventionist approach to self-inspection in place?

Increasing complexity (and coupling) in manufacturing processes and arrangements warrants a critical review of self-inspection activities

- Self-inspection programmes do not appear to have evolved accordingly to ensure that they are capable of delivering effective oversight as complexity and coupling increases

Better self-inspection programmes could not only help ensure compliance and drive continuous improvement, they should help deliver substantial benefits to companies in the changing regulatory environment that is ICH Q8, Q9 & Q10

- Risk-based regulatory oversight & regulatory flexibility is possible
- But Self-inspection has received little focus or attention in recent years
- More 'cool' topics (Quality Risk Management, Quality by Design, PAT) have been in the spotlight



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# Current GMP Requirements

The EU GMP Directives specifically require self-inspection programmes to be in place

- GMP Directives 2003/94/EU (H) and 91/412/EEC (V)
  - Repeated self-inspections are required
  - To monitor the implementation and respect of GMP
  - To propose any necessary Corrective Measures
  - Record-keeping requirements also

Chapter 1, on Quality Management, requires:

- “The QA System should ensure that there is a procedure for self-inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the QA system”.
- “QA ... covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organised arrangements...”
- *Product Quality Reviews*: There should be management procedures for the ongoing management and review of corrective and preventative actions and “the effectiveness of these procedures verified during self-inspection.”



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# Current GMP Requirements

Chapter 9 reflects the GMP Directives, and gives additional guidance:

- 9.1 Personnel matters, premises, equipment, documentation, production, quality control, distribution of the medicinal products, arrangements for dealing with complaints and recalls, and self inspection, should be examined at intervals following a pre-arranged programme in order to verify their conformity with the principles of Quality Assurance.
- 9.2 Self inspections should be conducted in an independent and detailed way by designated competent person(s) from the company. Independent audits by external experts may also be useful.
- 9.3 All self inspections should be recorded. Reports should contain all the observations made during the inspections and, where applicable, proposals for corrective measures. Statements on the actions subsequently taken should also be recorded.



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# Current GMP Requirements

For Active Substance manufacturing, Part II (2.4) states:

- In order to verify compliance..... regular internal audits should be performed in accordance with an approved schedule.
- Audit findings and corrective actions should be documented and brought to the attention of the responsible management.
- Agreed corrective actions should be completed in a timely and effective manner.



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# Current GMP Requirements

But the guidance in Chapter 9 and Part II (2.4) is fairly high-level, short and basic

- No guidance on the different types of self-inspection programmes that might be carried out, (e.g. horizontal, vertical, systems-based, process-based, departmental-based, etc.)
- No consideration given to process or system complexity
- No other risk-based provisions



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# Current GMP Requirements

- Certain areas that would be important to self-inspect are not mentioned in Chapter 9 or in Part II (2.4), e.g.
  - Qualification & Validation activities
  - Deviations Management
  - Change Control
  - Batch Release activities and arrangements
  - Arrangements in place with external Reg. Affairs for ensuring MA-compliance
    - e.g. communicating variation and manufacturing commitments
  - Warehousing and Goods-in checks
  - Qualification of Contract Labs and Manufacturers



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# GMP Deficiencies & Potential Recall issues

- It is reasonable to expect that certain deficiencies and potential recall issues should have been identified and averted if effective self-inspection programmes were in place

*For example:*

- Qualification of a contract manufacturer on the basis of an audit report performed by the company's Corporate Quality group in relation to a different product for a different site, and only QC was audited during that audit
- Cleaning procedures and practices not adhering to what was validated and lacking in sufficient detail to ensure that effective cleaning takes place
- Manufacturing processes differing substantially from what is registered in the Marketing Authorisation
- A tray-dryer is used to dry a granulate but a fluidised bed dryer is registered
- Stability studies promised at MA Renewal five years ago not being started



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# GMP Deficiencies & Potential Recall issues

- Deficiencies and recall issues contd.

- Recurring product mix-up issues on a packaging line, despite detailed line clearance procedures being in place and despite previous recall actions for similar issues
- Use of an unregistered source of heparin active substance for an Irish-marketed medicinal product
- Deviation investigations not effectively addressing batch quality issues despite well defined deviation procedures being in place
- Poorly designed process validation protocols resulting in batch homogeneity not being established for residual solvents in an active substance
- Batches being released with a packaging component stating an incorrect product strength despite multiple checks (up to 7) being in place
- Parallel importation activities not complying with the batch specific check requirements that apply to products with a Dual Pack Registration



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# Opportunities from critically reviewing one's Self-inspection programme

Self-inspection programmes require time and resources, and they should be value-adding

- A critical review of one's self-inspection programme can help determine whether:
  - The programme delivers thorough self-inspections
  - Self-inspections are performed in the right areas, at the right intervals and by the right people
  - The types of deficiencies that are being identified in regulatory inspections can also be identified internally, if present, during self-inspections
  - The types of issues that can lead to batch recalls and the cessation of batch release can also be identified internally, if present, during self-inspections
  - Opportunities for continuous improvement are identified during self-inspections, and can be realised thereafter
- In a mature QMS, Self-inspection should not be just about finding non-compliances
  - It should be evolving towards providing confirmation and verification that things are working well, that there is a high level of compliance, and that continuous improvement is in place



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# Three practical things to look at if doing such a critical review...

## 1. Is your self-inspection programme tailored to your site and to the specific arrangements and processes that are in place at your site?

- Often self-inspection plans are very generic
  - They could be applied to almost any site
  - They often do not reflect the specifics of your site –
    - the extent of use of contract manufacturers & external labs
    - the level of reduced testing in place at your QC lab
    - how your site interacts with Reg. Affairs staff to ensure MA compliance - Internal Reg Affairs Group or External?
    - the role of Corporate Quality, if any, in approving your suppliers
    - the use of contract QPs vs. in-house, permanent QPs
    - the complexity of some manufacturing processes over others
    - the level of HVAC expertise in-house
- *Self-inspection can add value and drive continuous improvement when it is tailored to your site and its specific manufacturing arrangements*



# Three practical things to look at if doing such a critical review..

## 2. Does your self-inspection programme help to assure the effectiveness of the site Deviation and Complaints Management Systems?

- Deviation and complaints management are key areas for Inspectors, as they are important indicators of the effectiveness of the QMS at the site
- Self-inspection can help identify if there is a tendency to assign “human error” as the cause for deviations, non-compliance incidents and complaints without proper justification
  - Often, human error is the symptom rather than the cause
  - Often also, staff may have little understanding of the factors that should be considered before human error is assigned as the cause of a deviation or incident
- Self-inspection can also help identify whether there is an over-emphasis on re-training as a preventative measure, as re-training may not prevent the incident from recurring
- *Self-inspection can add value and drive continuous improvement in these areas*
  - by identifying these high level issues before they become a problem
  - by ensuring education is provided if it is required



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# Three practical things to look at if doing such a review..

## 3. Is your self-inspection programme risk-based?

- Some of the self-inspection plans we see on inspection devote the same amount of time and resources to all areas, regardless of the level of complexity or risk in the area
  - July – QC Lab (1 Day, Two Auditors)
  - August – Non-Sterile Production (1 Day, Two Auditors)
  - September – Warehousing (1 Day, Two Auditors)
  - October – Complaints & Recalls (1 Day, Two Auditors)
  - November – Product Quality Reviews (1 Day, Two Auditors)
- It is important to take risk and complexity into account when designing your self-inspection programme
- ICH Q9 suggests some potential uses of Quality Risk Management in the area of *auditing and inspection*:
  - “Quality Risk Management may be used to define the frequency and scope of audits, both internal and external, taking into account factors such as:
    - *the complexity of the site*
    - *the complexity of the manufacturing process*
    - *the complexity of the product and its therapeutic significance.*”



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# Complexity & Coupling in Manufacturing Arrangements & Processes

Complexity issues come up time and again when one studies the application of risk management in other industries, but not so much in the pharmaceutical industry

- Process and system **complexity** are important attributes to consider when trying to understand:
  - *the reasons why non-compliances occur*
  - *why we have deviations within a Quality Management System*
  - *how they may be prevented in the future*
- The level of process and system **coupling** is also useful to understand, but is rarely looked at in GMP applications
- It will likely prove beneficial to start looking at these areas within GMP environments when designing the self-inspection programme



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# What is Complexity & Coupling?

- In the aeronautics field, much work has been carried out at NASA in an attempt to better understand the mechanisms by which failures and accidents occur
- NASA has worked to avoid accidents and failures in aerospace missions by reducing (or controlling) the extent of system complexity and coupling in their spacecraft and projects
- In complex and tightly-coupled systems:
  - Failures can be the result of many seemingly unconnected causative events
  - They can result from interactions that were not in the design intent of the overall system
  - The accident pathways that can occur are often complex and appear to have “an intelligence of their own”, exploiting circumstances that no engineer could reasonably plan
  - With complex systems, combinations of such events are “practically limitless,” and these cascading failures can accelerate out of control, confounding human operators and denying any chance of recovery
- *Ref. Michael A. Greenfield, “Normal Accident Theory - the Changing Face of NASA and Aerospace, NASA Office of Safety and Mission Assurance, November 17th, 1998.*
- *See also Perrow, C., Normal Accidents: Living with High-Risk Technologies, New York Basic Books, 1984.*



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# What is Complexity & Coupling?

NASA has described **complex** systems as systems with:

- Design features, such as branching and feedback loops
- Unfamiliar, unplanned, or unexpected sequences which are not visible or not immediately comprehensible
- Opportunities for failures to jump across sub-system boundaries

NASA has described **tightly-coupled** systems as having:

- Time dependent processes that cannot wait
- Rigidly ordered processes, as in Sequence B must follow A
- Only one path with a successful outcome
- Very little slack in the system, as the system requires precise quantities of specific resources for successful operations

*Working to reduce the level of process and system complexity and coupling at NASA was a major part of their Risk Management programme from the late 1990s onwards*



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# Can looking at Complexity & Coupling benefit the GMP Environment?

It is not likely that the GMP environment is any more immune to the adverse effects and problems posed by complexity and coupling than other industries have been

*Take change control activities relating to medicinal product packaging:*

- e.g. changing an antidepressant package leaflet and SPC to add suicide warnings

*In some companies, these activities can sometimes be **highly complex***

- They can require the input of several different groups and people for the co-ordination, assessment, review, approval, and implementation of the proposed change.... not to mention the input of regulatory agencies and off-site printing companies as well

*Such activities are also often **tightly coupled***

- There are usually strict timelines to be adhered to for each part of the process
- Specific interactions have to take place in a certain order, to allow the packaging change to be implemented in a compliant but economically viable manner
- Such interactions may include those between regulatory affairs and manufacturing personnel, between regulatory affairs and marketing groups, and between regulatory affairs and medical information staff in order to communicate and schedule manufacturing, marketing and medical information activities for the changed packaging or labelling component



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# Can looking at Complexity & Coupling benefit the GMP Environment?

Many recalls occur when such change control activities fail, e.g. when companies fail to implement key safety variations to package leaflets and product labelling in the agreed timeframe

- In Market Compliance at IMB, we investigate such issues via the Quality Defect & Recall programme. In some serious cases we find that:
- The procedures and systems in place for managing packaging and labelling changes are:
  - Highly convoluted, with many different groups involved
  - Have many time-dependent inter-dependencies
  - Are subjected to very tight timelines
    - In essence, they could probably be described as being *highly complex* and *tightly coupled*
- Sometimes, there can be a poor understanding within the company of how the change control system actually operates for such changes
  - For example, regulatory affairs staff involved in packaging-related changes were not always aware of other key groups within the same company that were also highly involved in the implementation of such packaging changes
- *It is clear that a reduction in system complexity and coupling would be of benefit*



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# How does this relate to self-inspection?

Getting an understanding of complexity and coupling will likely help ensure that your self-inspection programme can be designed to take into account the extent of system / process complexity and coupling that may be present

- Self-inspection programmes and plans can thus be made more risk-based
- Self-inspection resources can be targeted at those higher risk areas
- Detailed **Process mapping studies** can help determine which processes and systems are highly complex and coupled
- At IMB, we have benefited from this approach
  - e.g. by Process Mapping the **Sampling & Analysis Process** using a swim-lane approach
    - Many improvements have been made in this process over the last few years
    - Backlogs and problems with the process have been substantially reduced
    - This is allowing for the better use of laboratory and staff resources



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# Can self-inspection deliver benefits in the ICH Q8/Q9/Q10 Regulatory Environment

- The ICH Q8, Q9 & Q10 initiative is driving the regulation of pharmaceuticals towards an environment that is:
  - **More science-based** (ICH Q8 – Pharmaceutical Development)
    - emphasising a greater focus on process and product understanding
    - potential for less regulatory oversight when changes are being made
  - **More risk-based** (ICH Q9 – Quality Risk Management)
    - allowing for risk factors to drive decision-making and other activities, such as batch release, end-product testing, qualification, validation, the extent of regulatory oversight by inspectors and assessors...
  - **More Quality System-based** (ICH Q10 – Pharmaceutical Quality Systems)
    - emphasising increased management responsibility and the need for continuous improvement across the product life-cycle
    - more like the ISO 9001:2000 approach to Quality Management Systems



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# Can self-inspection deliver benefits in the ICH Q8/Q9/Q10 Regulatory Environment

- ICH Q9 was an important milestone in the development of the pharmaceutical regulatory and GMP environment
  - ICH Q9 indicated the formal acceptance by GMP regulators of risk-based approaches
  - A “**deterministic**” (or fixed rule) approach to GMP is not the only way to do things
  - ICH Q9 presented potential mechanisms for reduced regulatory oversight and risk-based decision-making
    - “ ..... effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company’s ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight.”
    - “ ... quality risk management can facilitate better use of resources by all parties.”
- ICH Q10, finalised June 2008, makes provision for reduced regulatory oversight also
  - Annex 1 presents scenarios with potential opportunities to enhance science and risk-based regulatory approaches
  - ***Demonstrating*** that an effective pharmaceutical quality system is in place, including the effective use of quality risk management principles, presents an opportunity for an increased use of risk-based approaches to regulatory inspections



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# ICH Q8/Q9/Q10 Regulatory Environment cont'd

- Demonstrating that an effective pharmaceutical quality system is in place would be a key requirement in this area
  - It is unlikely that Inspectorates would be willing to consider applying reduced oversight to a company without evidence that an effective pharmaceutical quality system is in place at that company
  - A PIC/S Expert Circle on Quality Risk Management is working on developing guidance for Inspectorates for risk-based inspection planning and other related areas
    - Applying the ICH Q9 & Q10 provisions is a significant part of this work
    - e.g. recognising the four specific Pharmaceutical Quality System elements that were identified by ICH Q10 as being important
      - The Process Performance and Product Quality Monitoring system
      - The CAPA system
      - The Change Management system
      - Management review of process performance and product quality
  - *The results of self-inspections are important in these areas, see ICH Q10*



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# ICH Q8/Q9/Q10 Regulatory Environment cont'd

- How might a company demonstrate that an effective pharmaceutical quality system is in place?
  - The outcome of regulatory inspections will of course be an important factor
  - But it is probable that one cannot conclude that an effective pharmaceutical quality system is in place without having assessed the effectiveness of the self-inspection programme - a major element of the QMS
    - Inspectors do not normally review self-inspection reports, and as a result, may not be in a position to directly assess the effectiveness of the self-inspection programme
  - There are probably **opportunities for companies** who take a proactive role in demonstrating to their Inspectors the effectiveness of their self-inspection programme



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# Demonstrating that an effective self-inspection programme is in place

The current situation is that most companies consider self-inspection reports as being off-limits to Inspectors

- Inspectors *are* legally empowered to review the contents of self-inspection reports, but choose not to do so unless it is absolutely necessary
- The reasons for this were well founded, and are still well founded... but this policy has probably led to some negative outcomes:
  - The time and resources devoted to self-inspection activities in some companies may be too low
  - Given all the other important things that need doing, ensuring that a good self-inspection programme is in place may be low on the list of priorities when it is known that inspectors will not review the reports anyway
  - The commitment of senior management to self-inspection in some companies may be too low
  - Inspectors only normally review the self-inspection procedure and plan, and verify that the planned self-inspections have actually been carried out...
    - Inspectors normally do not assess the effectiveness of the self-inspection programme



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# Final Thoughts & looking towards the future...

*The IMB is not intending to change its current inspection approach to self-inspection*

- This talk was intended to raise the profile of self-inspection in GMP environments
  - To outline the importance of effective self-inspection programmes with a view to promoting compliance and reducing the occurrence of product recalls
  - To set out some thoughts for consideration about critically examining your self-inspection programme and about complexity & coupling in processes and systems
- But ICH Q8, Q9 & Q10 are driving changes in the regulatory and GMP environments
  - Competent Authorities are working to implement the concepts of Q8, Q9 & Q10
  - Some parts of the EU GMPs have already been changed as a result
  - It is an opportune time to identify ways in which the potential benefits of ICH Q8, Q9 & Q10 may be realised at a practical level
    - Improvements in self-inspection may prove to be important in this context!

*A critical examination of your company's self-inspection programme may deliver unexpected benefits as we all work towards the implementation of ICH Q8, Q9 & Q10!*



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# Questions / Discussion?



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