Quality Metrics
Regulatory Perspective

Presented by: Karen Ginsbury
For IFF, Denmark
March 2014
Background

• MHRA Compliance reports and risk based inspections – since 2009 / 10
• Early 2013 FDA asked industry and public for input to use of quality metrics
• Let’s take a look
Risk Based Inspection Process (MHRA)

An objective inspection planning process that allows the relative risk of sites to be determined and a suitable re-inspection period set to ensure proportionate surveillance
Overview of the process

• Sites come under the system following their first inspection after April 2009

• There was no retrospective review of sites although current inspection dates have been set based on previous procedures/assessments.

Key changes in the inspection planning/review process are:

– A Compliance Report is completed by sites prior to the inspection and returned to the inspector
Overview of the process

– Inspectors determine the risk rating post inspection by completing an annex to the full inspection report
– The full inspection report is issued to all inspected sites
– Sites provide Interim Updates of changes between inspections
– Interim Updates and any other live intelligence is assessed by inspectors and impact on next inspection date determined
Compliance Report

- Input to the inspection: requires sites to report significant changes in Performance, Staff, Ownership, Processes/Products, Facilities/Equipment or Other
- Signed by CEO/ Site Director/ Managing Director – demonstrates commitment to the current status of changes affecting the organisation by the person responsible for approving funding for the site.
- Sites submit to the inspector at least 5 working days prior to the inspection
- Sites define what they regard as ‘significant’ but guidance and examples are provided on the MHRA web site
- The Compliance Report will be reviewed during the inspection
The Annex allows inspectors to assess the risk level of the site based on the following parameters:

1. Inspection deficiencies raised:

<table>
<thead>
<tr>
<th>Risk rating level</th>
<th>Input from current Inspection Findings (last inspection findings applicable to rating V only)</th>
<th>Provisional rating – this assessment</th>
<th>Final rating Last Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Serious triggers outside the inspection cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Critical finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>$\geq 6$ Major findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>$&lt;6$ Major findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>No critical or Major findings</td>
<td></td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>No critical or Major findings from current or previous inspection and $&lt;6$ other findings on each.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## 2. Discriminatory Factors:

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>None relevant (default)</td>
<td></td>
</tr>
<tr>
<td>Significant concern over robustness of quality system to retain adequate control</td>
<td></td>
</tr>
<tr>
<td>Significant failures to complete actions to close previous deficiencies raised at the last inspection.</td>
<td></td>
</tr>
<tr>
<td>Significant nature of future changes on site</td>
<td></td>
</tr>
<tr>
<td>Complex site</td>
<td></td>
</tr>
<tr>
<td>Significant changes reported in Compliance Report</td>
<td></td>
</tr>
<tr>
<td>Higher risk rating identified by other GxP and considered relevant to the GMP site</td>
<td></td>
</tr>
<tr>
<td>Site cause recalls or rapid alerts since last inspection</td>
<td></td>
</tr>
<tr>
<td>Nature of batch specific variations submitted since the last inspection give concern over the level of control.</td>
<td></td>
</tr>
<tr>
<td>Regulatory action related to the site</td>
<td></td>
</tr>
<tr>
<td>Significant mitigating factors applied by the site</td>
<td></td>
</tr>
<tr>
<td>Failure to submit interim update and/or failure to notify MHRA of significant change or slippage in commitments.</td>
<td></td>
</tr>
<tr>
<td>Other discriminatory factor (record details and justify below)</td>
<td></td>
</tr>
</tbody>
</table>
These combined give the final risk rating/inspection frequency:

<table>
<thead>
<tr>
<th>Risk rating level</th>
<th>Inspection Frequency</th>
<th>Inspector Proposed Risk Rating (Y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Immediate (as soon as practicable)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 monthly</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>24 months</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>30 months</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>30 months with 50% reduction in duration of the next inspection</td>
<td></td>
</tr>
</tbody>
</table>
Frequency of Reinspection

• Any proposed frequency shorter than the standard 2 years subject to peer review / approval by a GMP Expert Inspector or a GMP Operations Manager prior to final reporting
Interim update

• Compliance report and interim update
Sites will be required to complete a Compliance Report in advance of inspection, this will be prompted by the inspector and these can be found on the right hand side of this page for download. A guidance document and example reports are also available to assist completion. The Compliance Report should be returned to your inspector prior to the inspection.

• Compliance Report Interim Assessment form is available for download and the guidance document for the Compliance Report applies. Instructions for return are contained on the form
Section 2 Changes since the last submitted Compliance Report (or last inspection)

Please provide information on site changes that the MHRA should be aware of in conducting a GMP compliance risk assessment of the site. Please add additional numbered pages where required but do not attach reports or procedures.
See guidance document for further information.

A decrease in complaints of 40% to 25 for the year ending Dec 07 has been noted through management review meetings, while an increase by 30% to 30 in non conformances raised in the sterile products suite has been seen in the same period.

An 40% increase in outstanding CAPA to 43 items has been seen as a result of resignation of 2 key staff, these have been re-prioritised but some key issues identified through self inspection may take 3 months longer to complete than we would have desired.

The Site Director has been replaced by X and 10 new Operators and one new supervisor have been recruited to support manufacture and packing of new product X.

An increase in overtime has recently been introduced to meet higher than expected demand on Product Z.

A further packaging line has been installed for packing new product X.
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An increase has been seen in non conformances across the site from 54 per year to 79 per year against a steady product/batch volume.

Two non conformances have been raised for issues that we regard as critical. One related to a cross contamination of a batch due to addition of an amount of an incorrect API. The other was due to identification of rogue tablets of product Z in a blister run of product Y.

Two packaging line supervisors retired and replaced by internally promoted Operators.

Product A no longer manufactured on site. Product B has been transferred from Site Z.

No changes in facilities or equipment.
Example – GMP Compliance Report

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Please provide information on site changes that the MHRA should be aware of in conducting a GMP compliance risk assessment of the site. Please add additional numbered pages where required but do not attach reports or procedures. See guidance document for further information.

Temporary closure of the unit at Site A has required a 50% increase in manufacture of Products X, and Y since January and will run until July. Some staff transferred from site A to help meet demand.

Change of work pattern to fit in manufacture for both sites.

New autoclave installed January currently being qualified and expect to go live July.

New Chief Pharmacist started.

Funding for site in the calendar year reduced by 10%.
Example – GMP Compliance Report

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MHRA website has...

• Industry guidance
• Examples of Compliance Report - Compliance Report
• Compliance Report Interim Update
• An introduction to the Risk Based Inspection process
  at the following location:

Risk Based Inspection Elements

• New sites to be automatically Risk rating II
• 6 Majors – is automatic cut-off for risk rating
• Not yet seeing enough interim updates

Industry feedback
• Like the process – simple to understand and use.
• Guidance documents and examples good.
• Visibility of risk rating/rationale appreciated.
• Approving signatories on the Compliance Report too remote from operations?

Retain – aim to involve those that fund compliance rather than responsible for compliance (e.g. QPs)
MHRA Statistics on Risk Based Approach
Nov 2009

<table>
<thead>
<tr>
<th>Risk Rating</th>
<th>Percentage</th>
<th>Inspection Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Rating 0</td>
<td>0%</td>
<td>Immediate re-inspection</td>
</tr>
<tr>
<td>Risk Rating I</td>
<td>3.2%</td>
<td>Re-inspect within 6 months</td>
</tr>
<tr>
<td>Risk Rating II</td>
<td>12.1%</td>
<td>Re-inspect within 12 months</td>
</tr>
<tr>
<td>Risk Rating III</td>
<td>47.6%</td>
<td>Re-inspect within 24 months</td>
</tr>
<tr>
<td>Risk Rating IV</td>
<td>37.1%</td>
<td>Re-inspect within 30 months</td>
</tr>
<tr>
<td>Risk Rating V</td>
<td>0%</td>
<td>Not functional until second cycle of inspections</td>
</tr>
</tbody>
</table>
Additionally the distribution of risk ratings for inspections closed off to the end of February 2010 is reported for information for industry:

<table>
<thead>
<tr>
<th>Risk rating</th>
<th>Description</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Immediate re-inspection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Re-inspection within 6 months</td>
<td>11</td>
<td>3.4%</td>
</tr>
<tr>
<td>2</td>
<td>Re-inspection within 12 months</td>
<td>55</td>
<td>17.4%</td>
</tr>
<tr>
<td>3</td>
<td>Re-inspection within 24 months</td>
<td>157</td>
<td>49.5%</td>
</tr>
<tr>
<td>4</td>
<td>Re-inspection within 30 months</td>
<td>94</td>
<td>29.7%</td>
</tr>
<tr>
<td>5</td>
<td>(not applicable until after second inspection under RBI)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

These indicate that approaching a third of sites will receive some regulatory relief from inspection while a half of all sites will remain on an inspection frequency equivalent to the previous standard.
MHRA Approach – Lots of Information and Transparency

Good Manufacturing Practice: Risk-based inspections

In this section...

- Background
- Good Manufacturing Practice (GMP) - Risk-based inspection process
- Compliance report and interim update
- Risk rating process

Background
Over the past three years, in the UK there have been significant developments in inspection risk management and the strategies of a number of regulators were reviewed by the MHRA.

It is considered that the scope, frequency and depth of inspections should be dependent on how the regulated organisation takes responsibility for compliance with the regulations. Whilst the company or organisation has always had legal responsibility for compliance, the notice of inspection has for some been a trigger for compliance assessment instead of a continuous compliance programme being in place.

Following a detailed review of risk-based inspection models used by a range of organisations, a draft model was designed to cover all GxP inspections, however, at implementation it is envisaged that there will be a different emphasis within the individual elements as appropriate to the different GxPs.

Good Manufacturing Practice (GMP) - Risk-based inspection process
The GMP risk-based inspection process commences for all participating sites on 1 April 2009. Participating sites are those UK sites that hold a manufacturing authorisation (MIA, MS, MIA (IMP)) and third Country sites that are named on a UK marketing authorisation or where UK has been the reference member state on a decentralised procedure.
FDA

• Asked industry and public about use of quality metrics to assist in evaluation of product manufacturing quality in order to:
  – Predict
  – Prevent
drug shortages
  and
  – As a tool for a risk based inspectional model
PDA /FDA Quality Metrics Conference and Points to Consider 2013

- FDA intent:
  - to establish metrics with clinical relevance to patients
  - Move to a more proactive quality assessment model for companies (continual improvement)
  - Move away from simplistic compliance based model
PDA /FDA Quality Metrics Conference and Points to Consider 2013

• Most metrics are lagging indicators
• Metrics need to move to leading indicators
• PDA position: monitoring trends is best for leading indicators and allows:
  – Early identification of control drift
  – Focus resources in a particular area
  – Performance based, continual improvement culture
Culture – difficult to develop measurable metrics

• Open and honest communication
• Clear vision and belief in quality
• Management leadership
• Management sponsorship of quality initiatives
• Listening
• Education
• Team approach to continuous improvement
PDA Approach

• Measuring quality needs a defined set of standards and requirements
• One set of standardized metrics can never be a surrogate for quality
• FDA should be cautious
• FDA should establish clear definitions
• FDA should consider cultural impact of identifying and collecting metrics
PDA Approach - Carrot

• Companies rewarded for demonstrating quality performance:
  – Preferred handling of Post Approval Change submissions
  – Reduced inspection frequency
Recommended Metrics for FDA Collection

**Trends per product**
1. Confirmed complaint rate
2. Batch reject rate
3. Confirmed OOS rate

**Trends per site**
1. Confirmed OOS rate
2. Batch reject rate
Important but difficult Metrics

(difficult to compare)

By Product
1. Process Capability
2. Critical investigations rate

By Site
1. CAPA effectiveness rate
2. Critical investigations rate
3. EM (excursions in A and B areas) rate
Focus

• Trends more reliable than single values
• Need to understand the context of the metric to use them properly – so don’t just submit numbers
• Variability
• Not absolute values and can’t compare between companies?
And that wraps up the regulatory

REGULATORS TEND TO FOCUS ON LAGGING INDICES