

# INTRODUCTION TO THE GMP RISK BASED INSPECTION PROCESS

Date 3<sup>rd</sup> November 2009

# GMP Risk Based Inspection process

## Definition:

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

All sites are regarded as GMP generally compliant unless action is taken against their license

# Goals of the Risk Based System

- Provide a risk based approach with minimal administrative impact to sites and inspectorate.
- Reduction of regulatory burden to industry by providing some relief from inspection frequency/ duration for compliant sites.
- Allow for greater surveillance (inspections) of less compliant sites.
- Principles consistently applied to both UK and third country sites.
- Take account of risk factors between inspections to amend next inspection due date as required.
- Meet Hampton requirements while maintaining appropriate controls within the EU requirements for GMP inspection cycle.

# Development of the GMP Risk Based Inspection Process

- The process was developed by MHRA during 2008 and 2009 taking account of:
  - Experience of other UK regulators e.g. H&S Executive, FSA.
  - EMEA Compilation of community procedures – “A Model for risk based planning for inspections of pharmaceutical manufacturers approach to Risk Based Inspection Planning”.
  - Previous risk based approaches to inspections within MHRA.
- The process was reviewed during development with a cross section of industry stakeholders via meetings in June 2008 and March 2009 and also through regular consultation with the wider GMP inspection team.
- The process was trialed on qualifying inspections planned during October 2008 – 25 sites participated providing a good cross section of review and feedback.

# Which Sites Do GMP Risk Based Inspection Apply to?

- ✓ All sites holding UK Manufacturing Authorisations (MIA, MIA (IMP), MS) including mixed human/veterinary sites.
- ✓ 3<sup>rd</sup> Country sites where UK is the supervisory authority for inspection.
- ✓ UK Sites holding a Blood Establishment Authorisation

It does **not** apply to:

- ✗ Active Ingredient manufacturers (voluntary or for cause inspection scheme via current EU directives)
- ✗ Blood Banks ( Risk assessed via an alternative process)
- ✗ Voluntary Inspections
- ✗ Contract Inspections (e.g. on behalf of EMEA, WHO, etc.)
- ✗ Contract Laboratories (covered under the GLP RBI system)

# Overview of the process:

- The system went live from 01 April 09, sites will come under this system following their first inspection after this date. 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 the sites prior to the inspection and returned to the inspector.
  - Inspectors determine the risk rating post inspection by completing a proforma 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.

# Key Steps – Requirements and Purpose:

- **The Compliance Report:**

- Input to the inspection by requiring sites to report *significant* changes in Performance, Staff, Ownership, Processes/Products, Facilities/Equipment or Other.
- Signature by CEO/ Site Director/ Managing Director etc. is required to demonstrate commitment to the current status of changes affecting the organisation – *by the person responsible for approving funding for the site.*
- Sites complete the compliance report and submit to the inspector *at least 5* working days prior to the inspection.
- Sites define what they regard as 'significant' - guidance and examples is provided on the MHRA web site.
- The Compliance Report will be reviewed during the inspection.

# Key Steps – Requirements and Purpose:

- The Inspection Report Annex 1:
  - The Annex allows inspectors to assess the risk level of the site based on the following parameters:
    1. Inspection deficiencies raised:

Risk rating level	Input from current Inspection Findings (last inspection findings applicable to rating V only)	Provisional rating – this assessment	Final rating Last Assessment
<b>0</b>	Serious triggers outside the inspection cycle		
<b>I</b>	Critical finding		
<b>II</b>	>/= 6 Major findings		
<b>III</b>	<6 Major findings		
<b>IV</b>	No critical or Major findings		
<b>V</b>	No critical or Major findings from current or previous inspection and <6 other findings on each.		

# Key Steps – Requirements and Purpose:

## 2. Discriminatory Factors:

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

# Key Steps – Requirements and Purpose:

These combined give the final risk rating/inspection frequency:

Risk rating level	Inspection Frequency	Inspector Proposed Risk Rating (√)
<b>0</b>	Immediate ( as soon as practicable)	
<b>I</b>	6 monthly	
<b>II</b>	12 months	
<b>III</b>	24 months	
<b>IV</b>	30 months	
<b>V</b>	30 months with 50% reduction in duration of the next inspection	

# Key Steps – Requirements and Purpose:

- Peer review:

- Any proposed inspection frequencies that are shorter than the traditional standard 2 year inspection frequency will be reviewed/approved by a GMP Expert Inspector or a GMP Operations Manager prior to final reporting.
- There is no formal appeal system, as previously complaints can be submitted – details on the MHRA web site.



# Key Steps – Requirements and Purpose:

- Interim Update

- The Interim update is similar to the Compliance Report but is used between inspections by the site to advise the inspector that actual significant changes have been made. These would be in the same categories as the Compliance Report.
- The Interim update is sent by e mail to the last inspector for the site copying the mail box [gmpinspectorate@mhra.gsi.gov.uk](mailto:gmpinspectorate@mhra.gsi.gov.uk).
- An Interim update is not required to be submitted where a Manufacturing Authorisation Variation has been submitted for the change in question as this will be assessed by the inspector anyway.
- The inspector will assess the changes and determine if an earlier or later inspection is necessary. Sites may not be informed of a change in inspection frequency until the inspection is arranged although inspectors will acknowledge by e mail the submitted compliance report.
- **The risk rating is not changed until after the next inspection (but inspection dates may be brought forward (or back)).**
- Subsequent Compliance Reports submitted before an inspection should therefore be simply a reference to the interim updates submitted since the last inspection.

## Use of Existing Elements of Risk Based Approach:

- Duration of inspections based on site size and extent/type of licensing as detailed on Manufacturing Authorisation(s).
- Inspection content based on standard approach plus particular areas of focus as determined by the inspector based on preparation.
- As always the inspector reviews and risk assesses findings throughout the inspection to determine course of action and direction of the inspection.
- Inspections with critical issues or other significant issues reported to the Inspection Action Group – generally follow up inspection within 6 months.
- Typically new sites followed up within 12 months - to inspect 'in action'.

# Industry Consultation during Development

- Stakeholder Meetings held in June 08 and Feb 09 with cross section of industry representatives; Large pharma, small pharma, NHS, industry bodies.
- Trial run of the RBI process in October 08, involving 25 sites ranging from small – large pharma, NHS, importers, herbals, 3<sup>rd</sup> Country.



# Comments/Questions from Stakeholders

The initial Compliance Report is too complex.

The process needs to be open and visible

We can see the benefits of a risk based approach to inspection planning

Why does the Compliance Report have to be signed by CEO or equivalent?

Will there be dialogue with inspectors on site?

More guidance is needed on the type of data to be reported

Will RBI data be available through Freedom of Information?

Sites have to be very compliant before getting significant reduction in inspection frequency/ duration

# Comments/Output from Trial Sites

The process was simple, the guidance was good

Will my information be available to others under FOI?

The Compliance Report could be more structured with specific prompts for information

How much detail do you want on performance reporting?

The update system could result in frequent notifications to MHRA

Easy to complete....  
Guidance notes simple

64% of the sites reviewed on the trial concluded a 2 year inspection cycle was required. Others spread fairly evenly between 12-30 months.

# Implementation

- The MHRA Web site has links to the relevant documents:
  - Industry guidance
  - Examples of Compliance Report
  - Compliance Report
  - Compliance Report Interim Update
  - An introduction to the Risk Based Inspection process
    - at the following location:

<http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/Guidanceandlegislation/Risk-basedinspections/index.htm>

# Post Implementation

- MHRA Seminar held May 09, presentations at numerous other industry seminars.
- Inspectors can provide guidance before and during inspections on the process.
- A formal review of the implementation and operation of the process was conducted by the inspectorate in October 09. A further review by non inspectorate staff will be conducted Q1 2010.
- A stakeholder meeting with industry representatives, industry bodies and NHS will take place on 24<sup>th</sup> November 09.
- It is planned to introduce minor amendments to the process from Q1 2010.
- Provide any comments on the process to your inspector following inspections.

# Statistics



Based on inspections *fully closed* to 19 Oct 09

Risk Rating 0	0%
Risk Rating I	0%
Risk Rating II	7.5% (re-inspect within 12 months)
Risk Rating III	57% (re-inspect within 24 months)
Risk Rating IV	36% (re-inspect within 30 months)
Risk Rating V	0%

# Feedback



## Sites:

- Like the process – simple to understand and use.
- Guidance documents and examples good.
- Visibility of risk rating/rationale appreciated.

## Inspectors:

- Appreciate openness of industry in completing compliance reports.
- Better records of inspection preparation.
- Simple easy to use system but very effective.
- Minor clarity of process needed in some areas.
- Not seeing the number of Interim updates yet that may be expected.



# Questions/ Comments?

See FAQs on MHRA web site:

<http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodManufacturingPractice/Guidanceandlegislation/Risk-basedinspections/Questionsandanswers/index.htm>

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