Risk Management of GMP Audits in Australia

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Topics

• General risk management of audits
• Risk approach to audit scheduling
• Risk approach to conducting an audit
• Risk approach to overseas manufacturers
Risk management of audits

- A risk based approach to GMP regulation must have a good foundation
  - Sufficient competent auditors
  - Effective management
  - Appropriate legislation
  - An effective Quality Management System
Risk Approach to GMP Audit Scheduling
Audit scheduling - context

- Wide range of product types:
  - Rx, OTC, complementary medicines, APIs
  - sterile/non-sterile
  - specific risks, eg highly potent, highly sensitising
  - potential for quality defects across all types
  - potential to cause harm varies according to type
Audit scheduling - context

• Different types of manufacturer:
  – size, number of sites
  – range of products
  – number of employees
  – steps of manufacture
  – complexity; eg automation
  – GMP knowledge
  – location
  – varying levels of GMP compliance
Audit scheduling - context

• Other knowledge:
  – compliance history
  – recalls
  – complaints
  – changes, eg key personnel
  – internal information, eg from dossier evaluation
  – external intelligence
  – results of TGA testing
Audit scheduling - context

• What we can control:
  – audit frequency
  – audit duration
  – size of audit team, including specialists
  – audit notice; announced vs unannounced (local only)
  – the audit plan; time spent on each activity
  – licence/certification issue
The Australian model assumes a relationship between GMP compliance and potential for product defect or failure:

- **Consequences** of product defect or failure depends on type of product
- **Probability** of product defect or failure depends on level of GMP compliance
Audit Scheduling – Risk Approach

• Manufacturers are profiled according to
  – type of product manufactured or type of manufacture
  – level of compliance after each audit
• This is used to determine *routine* re-audit frequency
## Examples of product risk classification

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>RISK RATING</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HIGH</td>
</tr>
<tr>
<td>Sterile medicines (including sterile APIs)</td>
<td>✓</td>
</tr>
<tr>
<td>Potent non-sterile medicines e.g. hormones some antibiotics, steroids, antineoplastics, etc</td>
<td>✓</td>
</tr>
<tr>
<td>Other non-sterile medicines including herbals</td>
<td>✓</td>
</tr>
<tr>
<td>Homoeopathics, minerals, vitamins, fish oils etc</td>
<td>✓</td>
</tr>
<tr>
<td>Sunscreens</td>
<td>✓</td>
</tr>
<tr>
<td>APIs (non-sterile chemical synthesis)</td>
<td>✓</td>
</tr>
<tr>
<td>Single Step: Sterilisers</td>
<td>✓</td>
</tr>
<tr>
<td>Label/pack</td>
<td>✓</td>
</tr>
<tr>
<td>Analysis/test</td>
<td>✓</td>
</tr>
</tbody>
</table>
Compliance classification

• **A1: Good Compliance**
  – few deficiencies, all of a relatively minor nature only. eg no critical or major deficiencies and less than 10 Others.

• **A2: Satisfactory Compliance**
  – few major or other deficiencies (but no critical), including relatively serious ones requiring objective evidence before close out and some of a relatively minor nature. eg 1-5 major deficiencies and more than 10 Others

• **A3: Basic Compliance**
  – a number of relatively serious major and other deficiencies (but no criticals), requiring objective evidence before close out, and some of a relatively minor nature. eg more than 5 major deficiencies

• **Unacceptable:** 1 or more critical, many majors
• Routine GMP audit frequency is determined using a matrix of product risk category and GMP compliance level:

<table>
<thead>
<tr>
<th>RISK CATEGORY</th>
<th>FREQUENCY IN MONTHS:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMP Compliance Rating:</td>
</tr>
<tr>
<td></td>
<td>Acceptable:</td>
</tr>
<tr>
<td></td>
<td>A1</td>
</tr>
<tr>
<td>High</td>
<td>24</td>
</tr>
<tr>
<td>Medium</td>
<td>30</td>
</tr>
<tr>
<td>Low</td>
<td>36</td>
</tr>
</tbody>
</table>
Audit Scheduling – Risk Approach

• Unacceptable GMP compliance:
  – risk assessment done (modified FMEA)
  – audit report and risk assessment considered by an internal, independent Review Panel
  – decision on a case by case basis
Audit Scheduling – Risk Approach

- Ongoing risk management
- The routine re-audit frequency may be modified at any time in response to post-audit information, eg:
  - recalls
  - complaints
  - internal information, eg dossier evaluation
  - external intelligence
  - results of TGA testing
  - Changes to manufacturer – e.g. key staff, relocation
Audit Scheduling – Risk Approach

• Possible action in response to post-audit information:
  – bring forward next routine audit
  – conduct a “special” (non-routine) audit - usually unannounced
  – request specific information/documentation from the manufacturer
  – include specialist in next audit team
  – etc…
Risk approach to conducting audits
Risk approach to conducting audits

• Auditors are “qualified” to do specific types of GMP audits
• Risk factors taken into account at time of planning, e.g. composition of audit team and audit duration
• Audits unannounced if justified on risk basis
Risk approach to conducting audits

- Deficiencies are classified on a risk basis, e.g. a critical deficiency is one that has produced, or may result in a significant risk of producing a product that is harmful to the user.
- Manufacturer’s response is risk dependent, e.g. objective evidence of corrective action expected for “major” deficiencies – description only for “others”.
- Close out audit may be conducted.
Risk approach to overseas manufacturers
Risk approach to overseas manufacturers

- Manufacturers in MRA partner countries
  - eg EU, Canada, Singapore
  - full confidence established
  - legally binding agreement delegating responsibility for GMP compliance decision
  - TGA audit not required
  - safeguard clause risk based:
    - an audit can be conducted if justified on a risk basis to the other party
Risk approach to conducting audits

- Manufacturers in non-MRA countries where there is some knowledge of the standard of GMP regulation:
  - eg PIC/S members, US FDA
  - agreement to exchange information only
  - TGA responsible for GMP compliance decision
  - decision made on a risk basis after reviewing key documents
  - TGA audits may be required at normal or reduced frequency
Risk approach to conducting audits

- Manufacturers in countries where there is little or no knowledge of the standard of GMP regulation
  - audits by MRA partner countries may be considered after review of key documents - unlikely to be accepted for high risk products. TGA audits may be required at normal or reduced frequency
  - all other audits must be conducted by the TGA
Summary

• The TGA has an effective risk based approach to scheduling and conducting audits.

• Reduced risk through good GMP compliance is recognised
  – industry benefits from lower audit burden
  – TGA benefits by being able to allocate limited resources according to possible risks to public health and safety
Thank you for listening!