Supply Chain Challenges and Risk Management

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21st April 2009
Supply Chain - Some Useful Guidance

Vendors – APIs and Excipients
- cGMP – Annex 8
- cGMP Chapter 7
- ICH Q7 (Actives)
- ICH Q9 (Risk Mgt.)
- PS 9100 (Excipients)
- FDA Good Importers Guidance (draft)
- FDA RiskMap

FDF Manufacturers
- Full GMPs
- ICH Q9 / ICH Q10
- MHRA Risk based compliance reports
- EMEA/192632/2006 – EU Risk Mgt Plan

Post Marketing Vigilance, GDP
- EU / TGA VOL 9a Pharmacovigilance Risk Mgt
- ICH Q9 (Risk Mgt.)
- Product review (GMPs Ch 1)
> 80% of all APIs sourced outside USA. (43% China, 39% India)

Would be greater than 80% for Australia

“Some generic supply lines have up to 15 different facilities in drug applications” – Janet Woodcock FDA

Since 1992 - 400% increase in “foreign” drug manufacturers

India has had a 25 times increase in imports to USA
Sharpened Focus by Regulators

• Trigger events:
  – Diethylene glycol excipient contaminated
  – OSCS contaminated Heparin (over 80 deaths)
  – Melamine in milk products
  – Lead paint in children's toys

• FDA response:
  – Wider inspection co-operation with EMEA and TGA for API plants
  – FDA Globalisation Act 2008 (draft)
  – FDA Initiative – Beyond our Borders
  – Permanent overseas FDA Offices (China and India)
    • Beijing, Shanghai and Guangzhou
    • 8 FDA officials
Some other recent concerns

- Internet based mail drug imports approx. 10mill / month in USA … estimated that many are counterfeited

- Asbestos in talc powder – Sth Korea 1200 products recalled

- Heparin OSCS issue re-surfaced in Ireland March 09

- Ranbaxy – stability data integrity (in dispute)
Different Agency Approaches to APIs

• TGA:
  – GMP Licensing of API manufacturers
  – TGA inspection to ICH Q7
  – FDF Manufacturers expected to have vendor assurance programs in place

• Europe:
  – ICH Q7 compliance responsibility of the FDF manufacturer
  – Qualified Person or agent must conduct GMP audit

• FDA:
  – Drug Master File (DMF)
  – Audits are product specific via (A)NDA
FDA Foreign Inspection 2002 -2007
(# firms estimated between 3249 and 6800)
FDA Globalisation Act 2008
(Proposed)

• Manufacturers of drugs and drug ingredients to test for contaminants (purity and identity)

• Restricted entry of products without detailed documentation

• Drug labels to identify the source of API and its place of manufacture.

• New enforcement provisions:
  – Extensive fines/prosecution for supplying misleading or false data to FDA ($100K - $150K each offense)

• Mandatory supply chain risk assessment reports for each Rx drug product to be made available to FDA.
Supply Chain - Country Risk Factors
(PWC Wider Risk Rating Asian Countries)
Moves to strengthen the supply chain

- Strengthen monographs eg glycerin, heparin
- Agency co-operation and foreign offices. Collaboration between FDA, EMEA and TGA (APIs)
- Mandatory 2 year GMP inspections by FDA?
- Test and verify/certify drug purity and identity
- Drug manufacturers required to develop risk assessment of the supply line - and presumably a risk control plan
- Manufacturers to take more responsibility
- Excipient oversight? Extremely challenging!
Possible Supply Chain Risk Factors

5. Parenteral/ Sterile / Biotech
4. Rx
3. OTC
2. Complementary
1. Excipient (???)

5. Known poor quality
4. Unknown history / New vendor
3. Known quality – OK
2. >10 batches, all OK
1. Long good supply history

5. No site assessment
4. No International GMP licenses
3. International GMP audits
2. QA reviewed
1. QA vendor audited >1 cycle
### Sorting Risks – where to input resources?

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<tr>
<th>Patient Risk / Severity</th>
<th>History x Profile</th>
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Some practical tips on managing Supply Chain risk

- Do not rely on documents alone
- Quality surveys provide only secondary information
- Have selection criteria based on risk, not price
- If possible go to site and audit thoroughly where there is any risk – conduct due diligence
- Should have a strong quality agreement – with penalties
- Conduct thorough receipt testing until satisfied
- Agree mechanisms for problem resolution in the quality agreement
- Insist on a strong problem resolution / CAPA culture
The difficult case of excipients

- PQG (UK) PS9100 guidance is helpful
- Excipient risks are driven by:
  - Dose form in which used (parenteral, oral etc…)
  - Function of the excipient
  - Inherent toxicity and quantity used in product
  - Potential for manufacturing cross contamination
- Practicality of auditing – may be problematic
- Which standards would apply in audit situation?
  - ISO 9001 / HACCP
  - Intermediate/basic GMPs
  - ICH Q7
China - Supply Chain

Figure 1  Growth of Total Output Value of China’s Pharmaceutical Industry (composed of seven sub-industries, at current prices)
(Unit: 100 million yuan)

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<th>Year</th>
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<td>2007</td>
<td>6,679</td>
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What is the value of a Government GMP Certificate?

- GMP Manufacturers Certificate valid for 5 years
- Audit team could be “good” or “bad” – impossible to be sure
- Local inspector(s) may expect co-operation from the manufacturers
- Length of audit is not a good indicator
- Non-conformances sometimes do not make sense to a westerner – (at least the English version)
Typical gaps and deficiencies

- Quality Systems often = more testing
- Facilities sub-standard finishes
- Validation often superficial
- Change control absent or document change only
- Failure investigation / CAPA superficial
- Limited risk management practiced
- Vendor management absent
- Feedback / Vigilance systems poor or absent
Compliance audit history - What to look for

- “Show” vs “Shadow” Manufacturing facilities
- International certification – TGA, EU, FDA etc.
- Recent audits by an international audit team
- Length of the audit (superficial vs extensive)
- Audit reports – did the group look beyond the quality manual and SOPs?
- Did the lead auditor have international experience?
A picture speaks a 1000 words

- Spend as much audit time in the factory as possible.
- Seeing is believing!
- Take a production record to the walk through
- Compare the production record to actual practices
- Walk the process(es) top to bottom
- Review in-process test stations
- Check what happens to rejects and reworks
What to expect when assessing documents

• Approx. 10 - 20% of the documents in English, usually with a Mandarin translation.
• Some key SOPs will be translated (maybe for the purpose of audit)
• Most quality documents/records are not accessible without a translator
• Technical files and foreign registrations should be in English
• A challenge to get the right information
• This significantly slows the audit down!
QUALITY POLICY  质量方针

精益求精，出类拔萃

金马医疗致力于在医疗诊断器械领域，
成为专业用家和企业买家的首选供应商。
金马医疗的每一位员工都要奉行全力完善运作流程，
遵从既定工作指引，追求零失误的服务和产品，
务求以出类拔萃的品质和精益求精的质量管理，
满足并超越顾客期望。
Example – critical device components

- Contract with parent company in Taiwan
- Parent sub-lets to sister company in China
- Chinese company sublets contract to local firm(s)
- All component marking indicate the product is supplied from Taiwan
- All documents/ test reports marked from Taiwan
- Impossible to fully trace the supply chain
- Situation would not be known without audit
Case Study – Quality Control

• Product quality delivered by intensive (and often 100%) inspection

• Almost all QC work is manual

• Quality management approach is basic – eg. no CAPA and no internal audit program

• Vendor defects are inspected out
  – > 20 - 50%+ component defects are common – are 100% sorted and rejected
  – Vendors are unreliable and indifferent to quality standards
  – Difficult to return faulty items
Case Study - Validation

- Understand the jargon – IQ/OQ/PQ
- Protocols contain little challenge and are minimal eg. “vendor provided certificate for IQ”
- Process validation not conducted – line is 100% inspected
- No risk assessment is applied
- Computer systems validation absent
- OK for Class CM but not for OTC or Rx products
• All the right words are in SOPs
• Focus is generally on correction and, occasionally, corrective action
• Preventive action not practiced well – weakness in RCA …. Poor close out on problems
• CAPAs generally not systematically analysed
• Risk analysis not applied to CAPA
Extremely challenging area! But improving
In Summary

• Vendor Quality is very variable = variable risk
• Do not rely on paperwork/documents alone
• MUST conduct due diligence BEFORE letting contracts
• Be very clear on quality standards in “Technical Agreements”
• Be prepared to visit / audit regularly
• Develop the relationship
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Thanks for Listening
Any Questions?