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Supply Chain Challenges and Risk Management

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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)

Global Drug Supply Landscape

- > 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 childrens 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

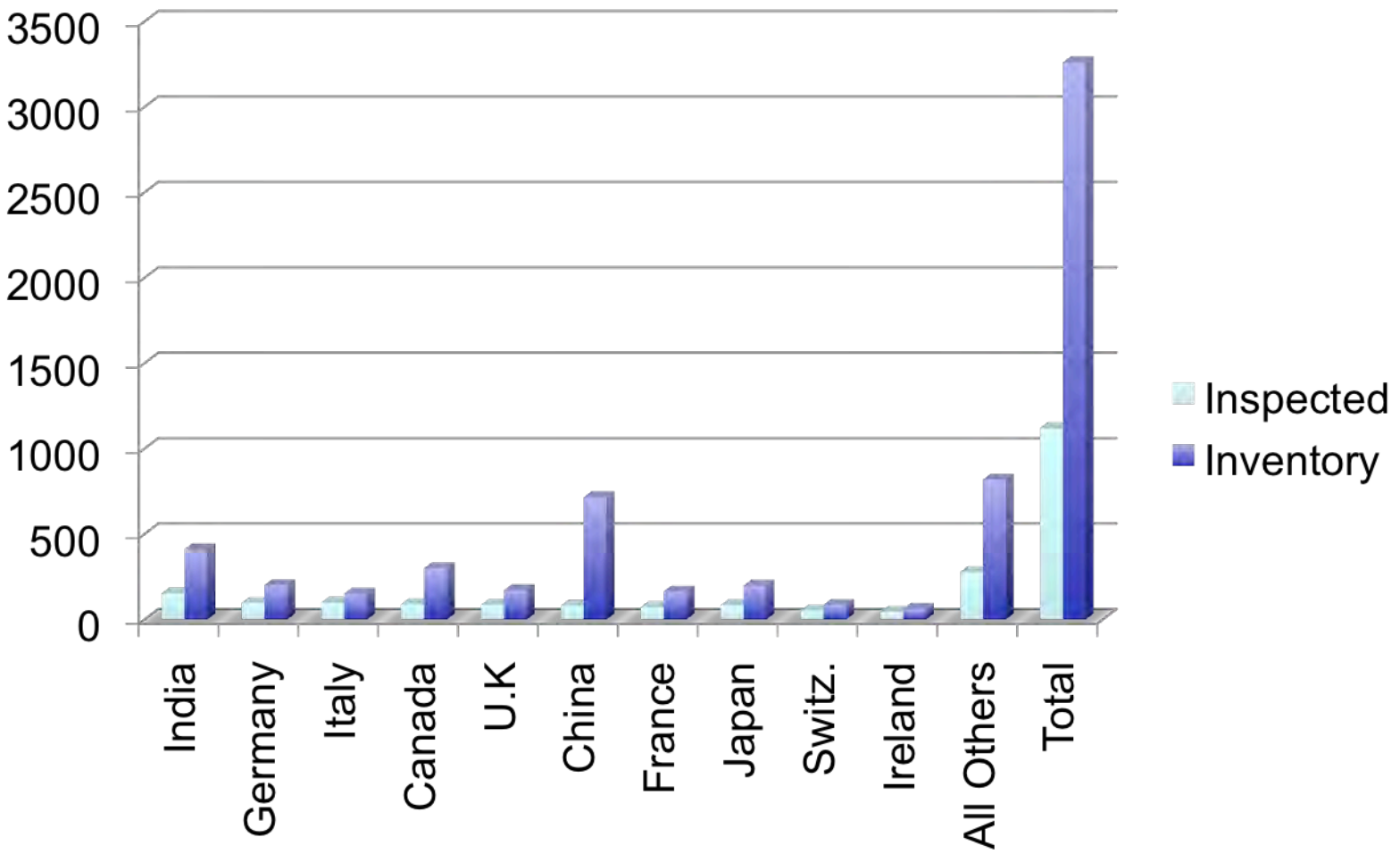
- Internet based mail drug imports approx. 10mill / month in USA … estimated that many are counterfeited
- Asbestos in talc powder – Sth Korea 1200 products recalled
- Heparin OSCS issue re-surfaced in Ireland March 09
- Ranbaxy – stability data integrity (in dispute)

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

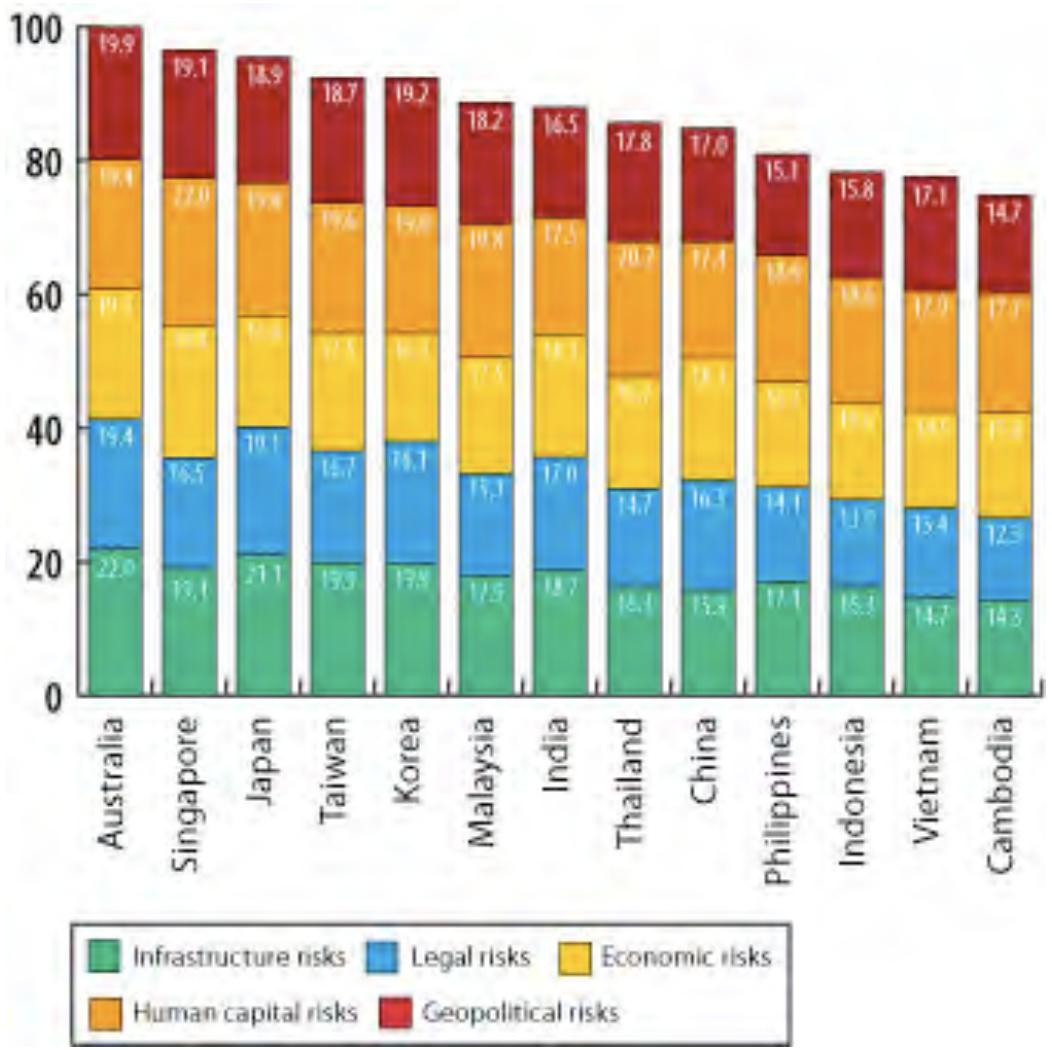
(# firms estimated between 3249 and 6800)



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

Patient Risk Factor

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

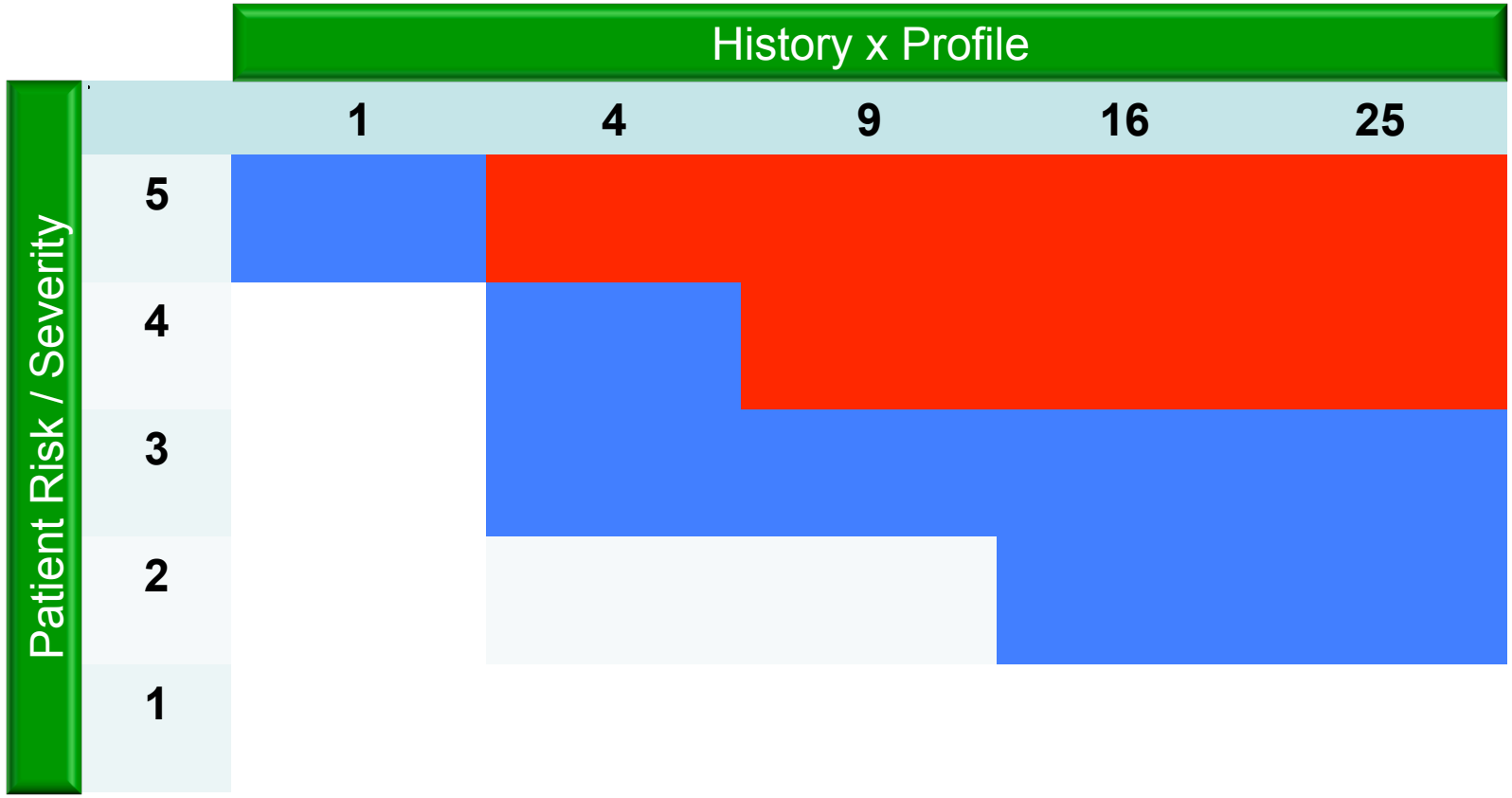
Supplier Quality History

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

Supplier Profile and Rating

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 ?



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

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献全力完善运作流程，
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

CAPA and Improvement Processes

- 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 ?