

# **Low Cost Countries**

## **China and India**

**The QP in the global context, November 2009**

# Contents

- Introduction
- Some industry facts for India & China
- Regulatory inspection perspective (US FDA, MHRA)
- The 'bad news' stories
- Counterfeits (briefly)
- Further insights
- Summary



# Intent

- Not going to refer to the role of the EU QP, relevant regulations etc.
- Nor why the focus is on India & China
- Intent is to paint a picture of the risks and opportunities in both countries.
- To give you some insights on how that risk might or might not change and some relevant factors which might influence it.

# India



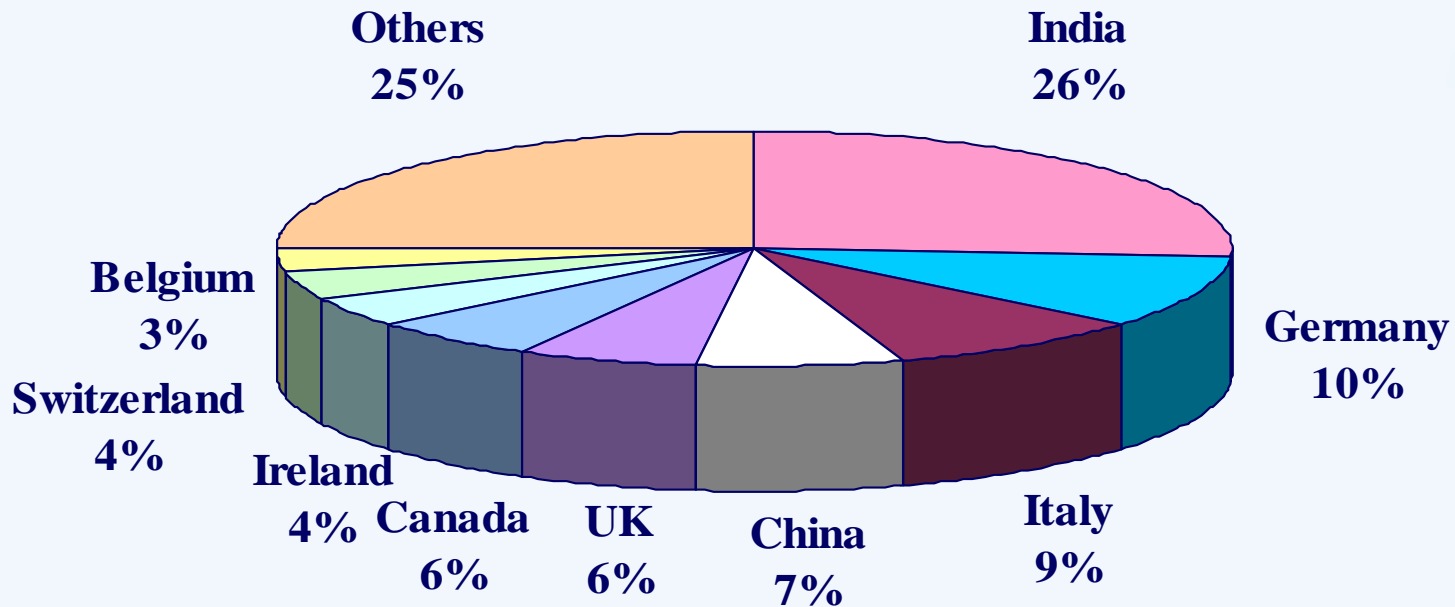
# India

- Has the largest number of 'FDA approved' plants outside the USA
- Estimated to be about another 50 FDA / MHRA standard facilities in the pipeline
- India produces approx. 25% of global generic drugs
- About 40% of India's production is exported (55% DP / 45% API)
- Domestic DP volumes are enormous, but are rarely made in the same plants as exports ('Export Only Units') due to strict price controls on domestic products (and different GMP standards).
- There are around 20,000 registered manufacturing units, but the top 250 supply 70% of the market
- Only 1 non-India based MNC (GSK) is in the top 10 companies in the industry

# India

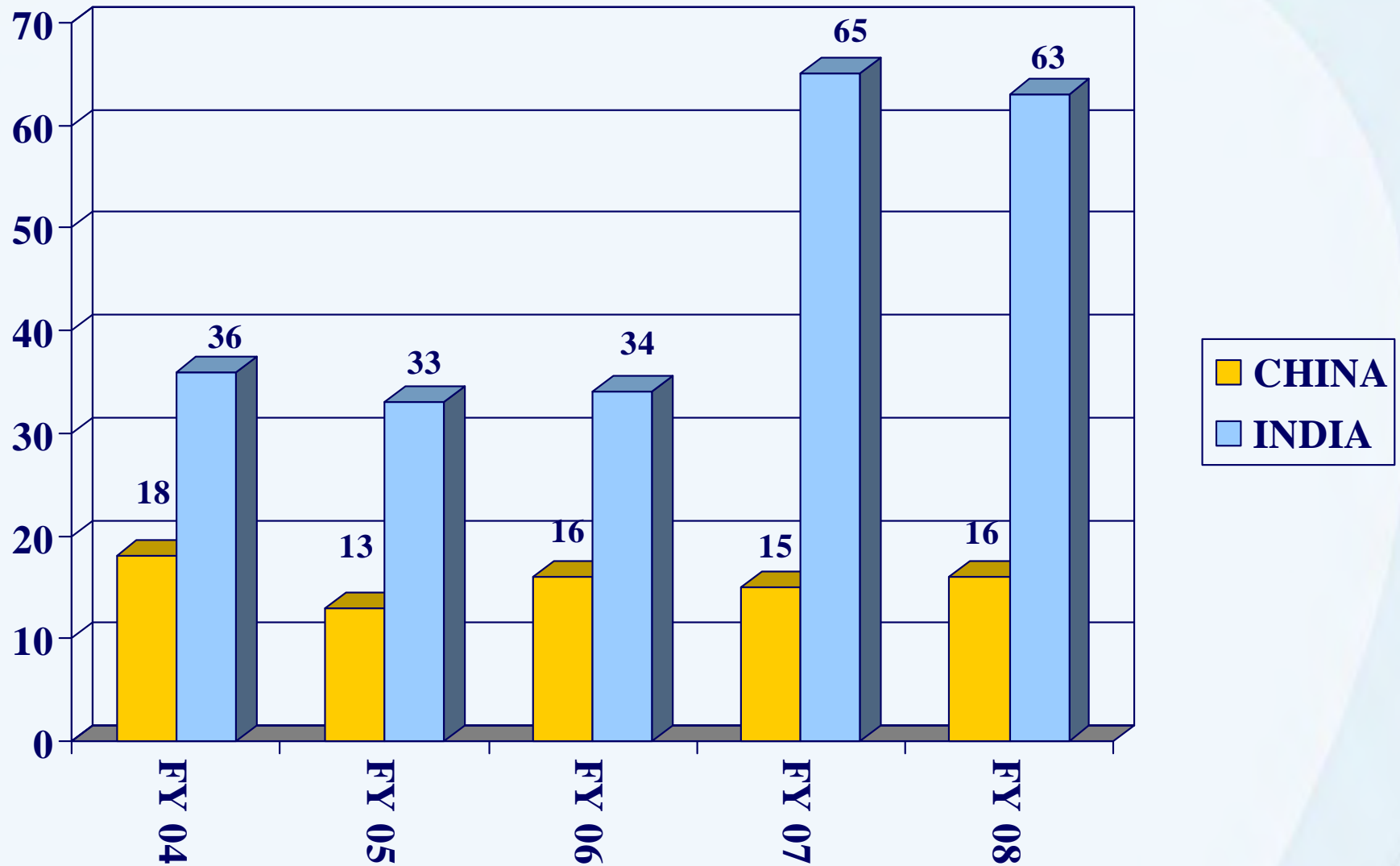
- Exports increasingly drive the industry – they already constituted \$3.2 billion of a total industry turnover of \$5 billion in 2005.
- Turnover expected to grow to \$25 billion by 2010 (McKinsey).
- The 2005-2010 'patent cliff' has offered a huge opportunity to Indian companies.
- India benefits from a pool of personnel with high managerial and technical competence and a skilled, highly educated workforce (also fuels huge local research capacity)
- The success story has been tainted by a few, relatively recent high profile 'bad news' stories.
- Indian GMP requirements / audits (domestic products) : Have not generally embraced systems / risk based approach to quality management. No apparent drive to harmonise with developed markets. Exporters initially rely on consultants to master FDA / MHRA / TGA etc. codes.

# US FDA Foreign Inspections in 2008 by Country

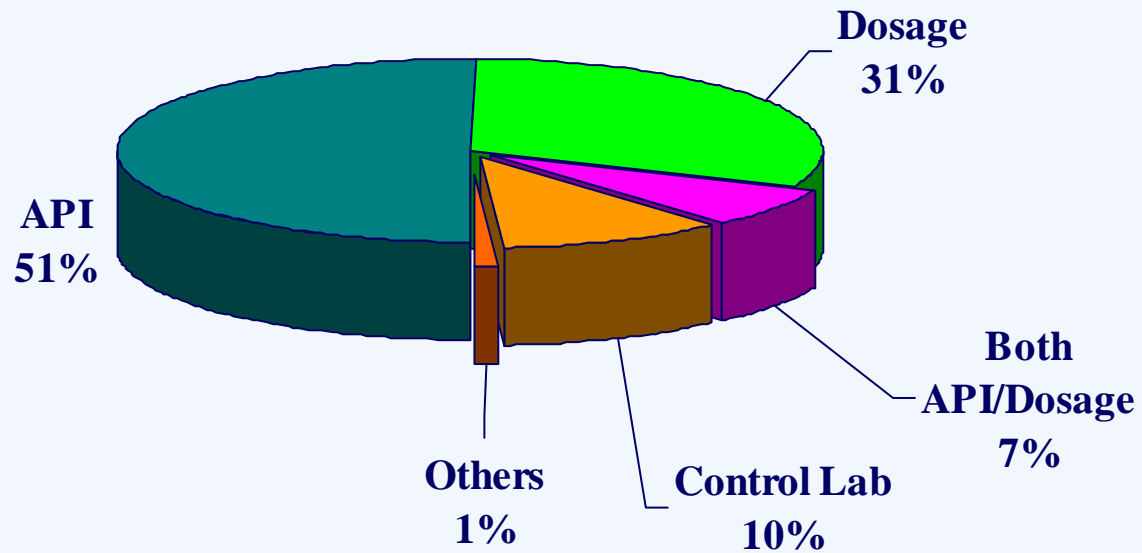


*(FDA Foreign Inspection Trends from presentations by US FDA's Brian Hasselbalch & Monica Caphart at the 2008 USA Southeast ASQ FDC/FDA Conference & the 2009 USA University of Georgia Annual GMP Conference respectively)*

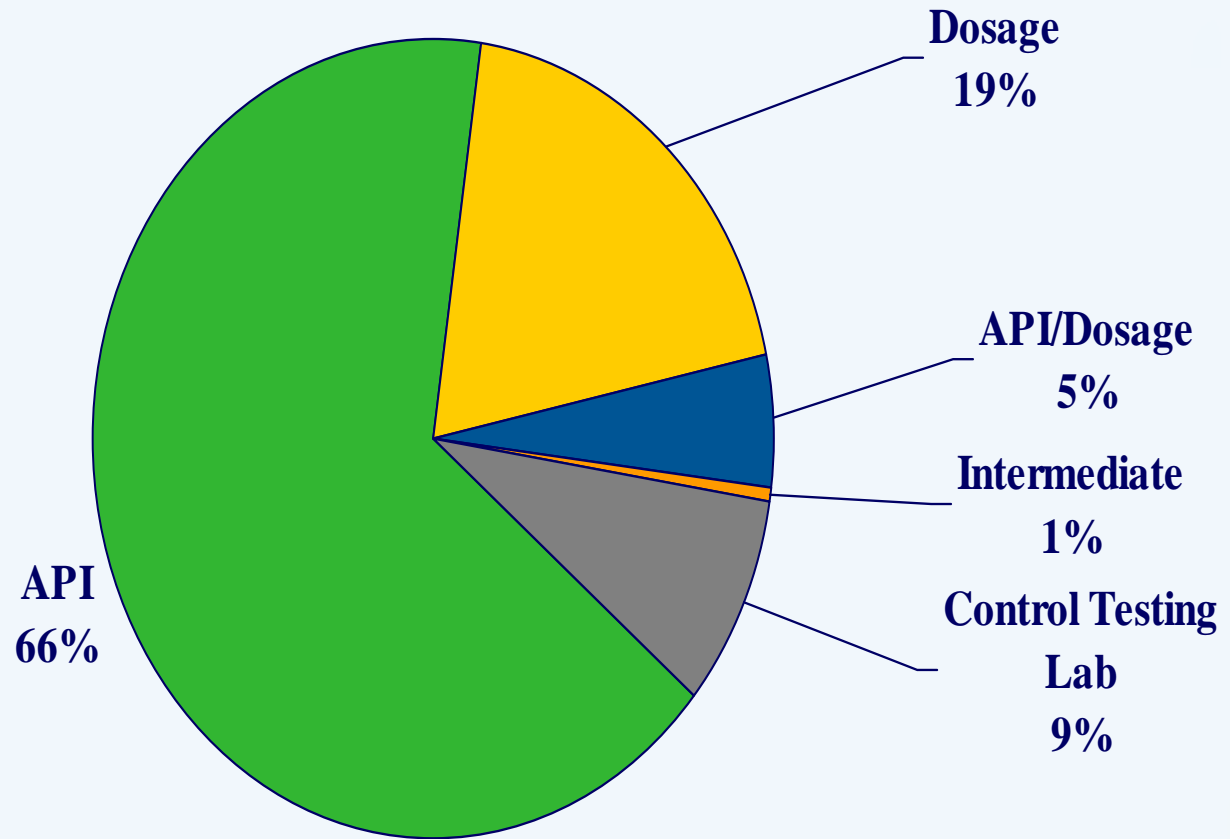
# US FDA Inspections in China and India FYs 2004 – 2008



# FDA Foreign Inspections in FY2007 by Firm Type

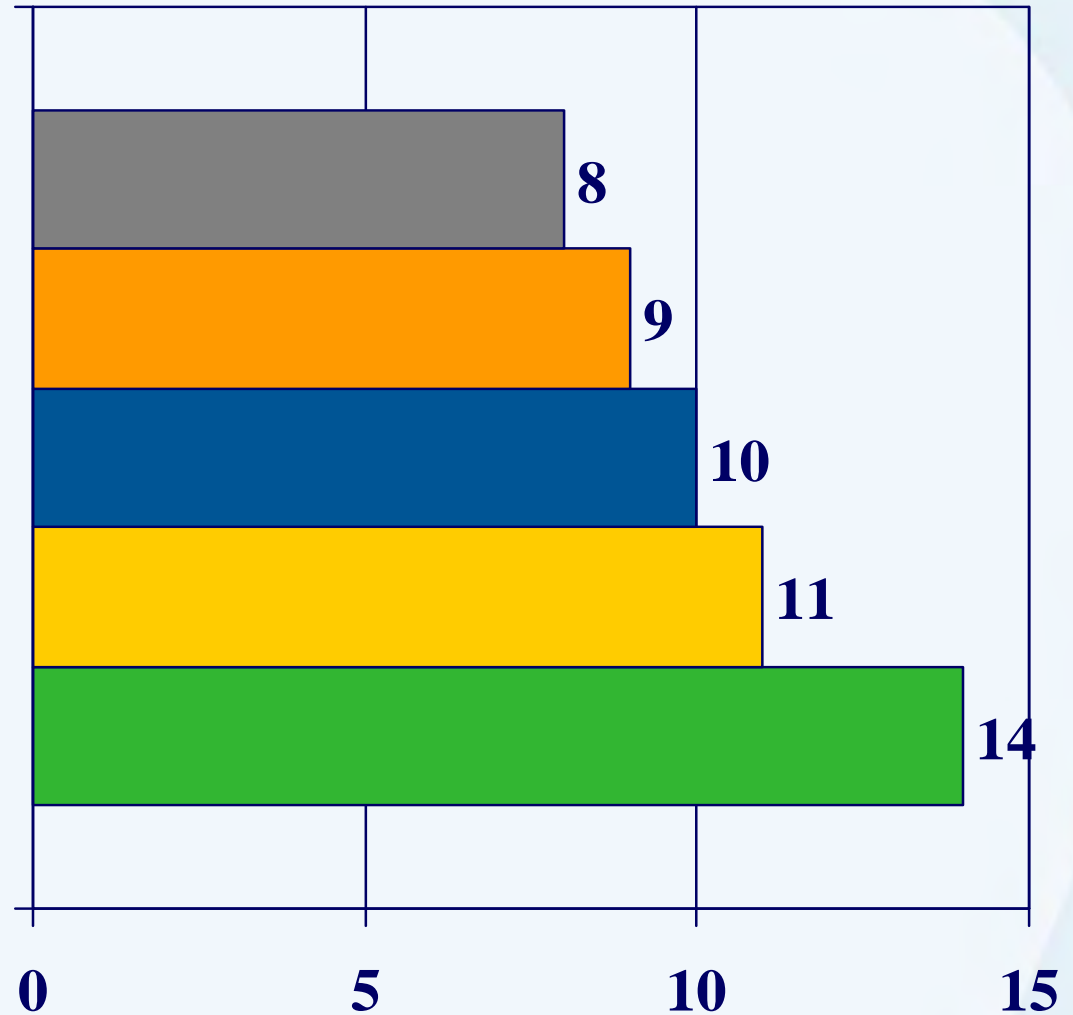


# Type of Manufacturing Facilities in India (FDA inspections 2004-2007)

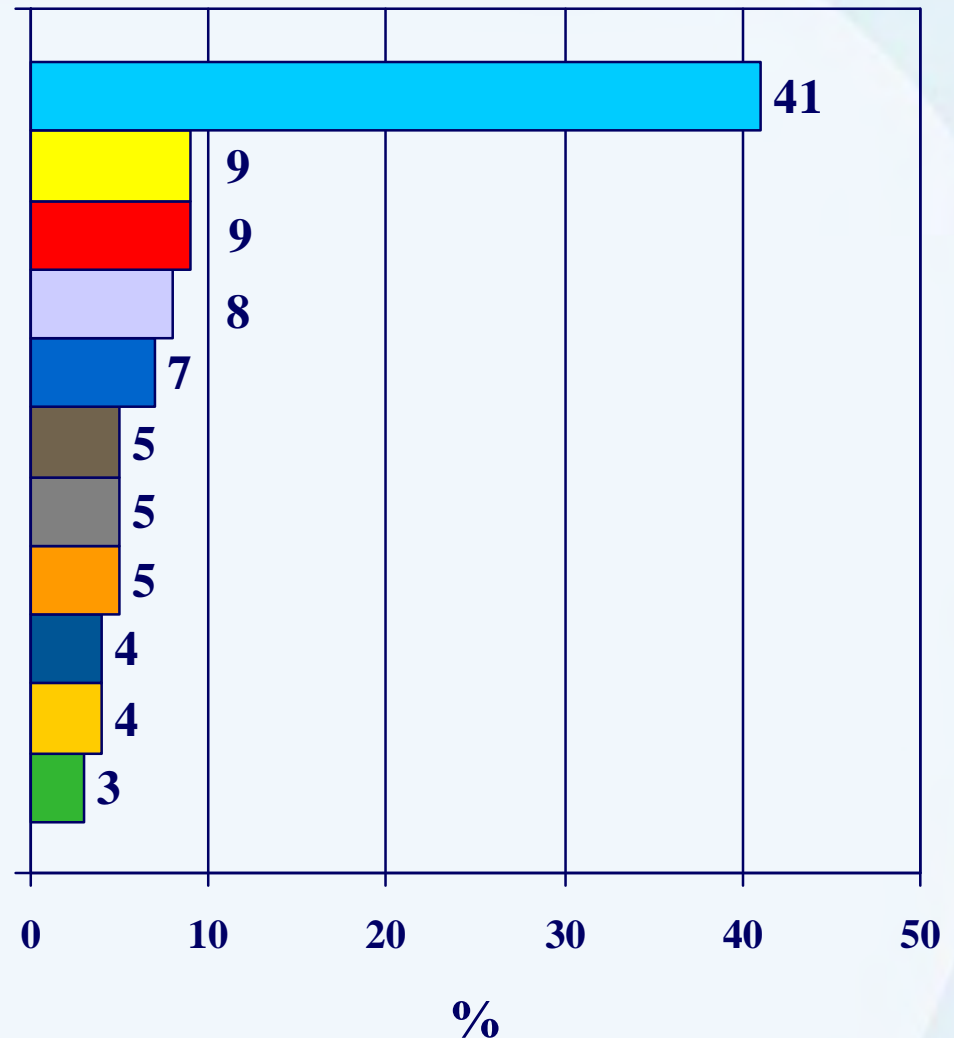


# US FDA Top Five GMP Deficiencies in India 2007

- **Equipment Cleaning/Maintenance, Cleaning Validation**
- **Lack of/Inadequated SOPs**
- **Equipment Design/Qualification**
- **Laboratory Records/Reports**
- **Laboratory Controls**



# US FDA Common GMP Deficiencies in India 2008



# 2007-2008 MHRA Inspection Trends

## **MHRA Top 5 Deficiencies (UK Domestic Inspections)**

1. Quality management
2. Quality system documentation
3. Batch release and QP duties
4. Environmental monitoring
5. Supplier and raw material control

## **MHRA Top 5 Deficiencies (Third Country Inspections)**

1. Potential for microbiological contamination
2. Design and maintenance of premises
3. Quality management
4. Environmental monitoring
5. Raw material control

## **MHRA Top 5 Deficiencies for QMS of API Manufacturers**

1. Lack of independence of the Production and quality functions
2. Insufficient systems for managing quality leading to inadequate assurance finished products consistently meet intended specifications
3. Internal audit programmes not achieved to agreed schedule
4. Annual product reviews not performed and issued in a timely manner
5. No corrective action as a result of OOS/RM/6003

# China



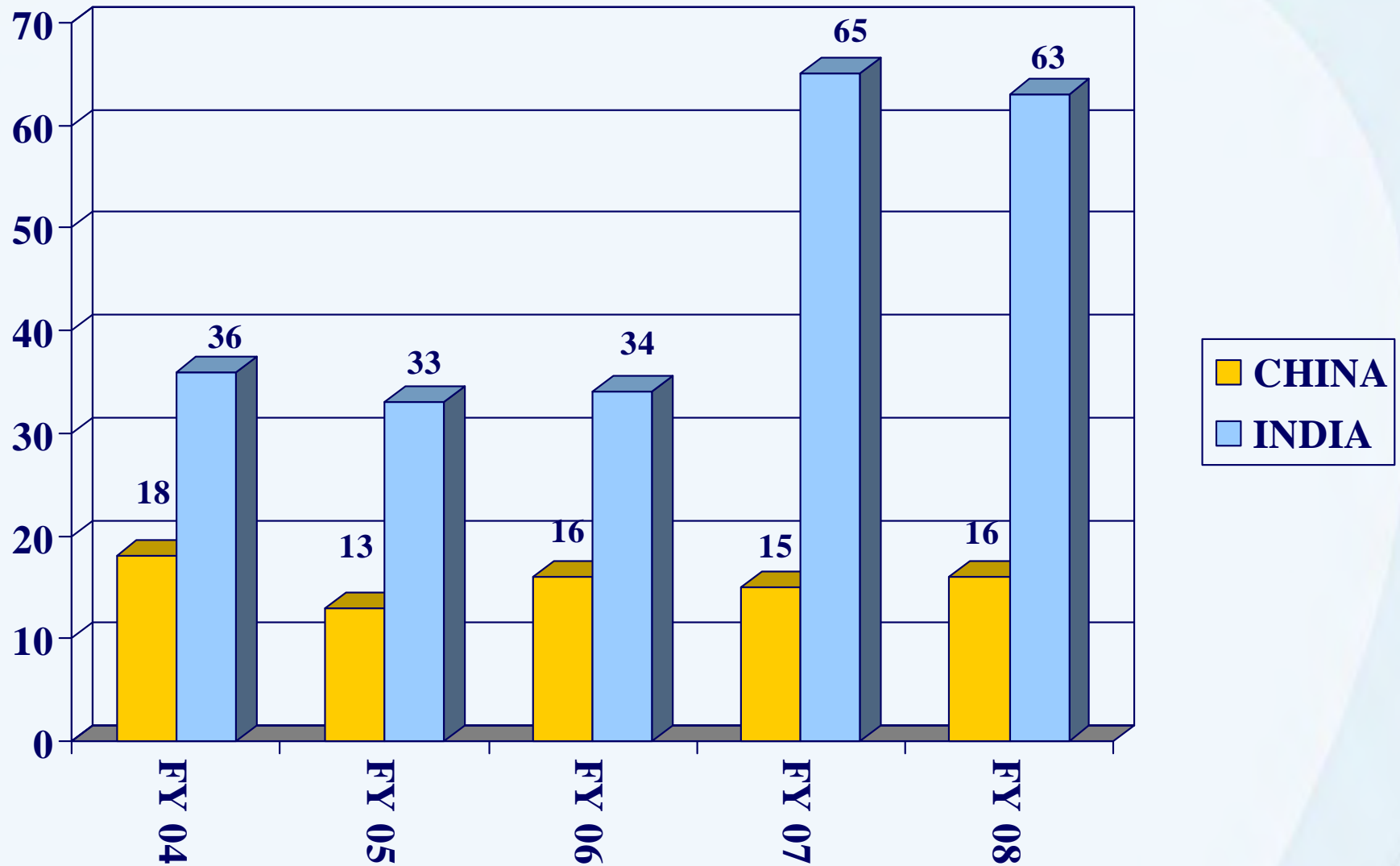
# China

- 2007 pharma industry sales \$94 billion (25% up on 2006)
- First half 2008 up another 19% on first half 2007
- Exports in first half 2008 were 10% of total revenue (compared to 40% for India)
- In 2007, domestic market split was 'chemical medicines' 54%, 'Chinese medicines' 24%, biologicals 9%.
- Domestic companies have 73% of market share, no MNCs in the top 10 companies. (J&J is the largest).
- Despite 'low cost' reputation, China has not been a major exporter, even of cheap generics.
- Lower research capability than India and slower to pick up on international norms and regulations.
- Also 'low' devices capability compared to developed countries.
- Strength in vaccines , due to long history of vaccinating local population.
- Domestic industry is geographically scattered and generally with outdated technology and management structure

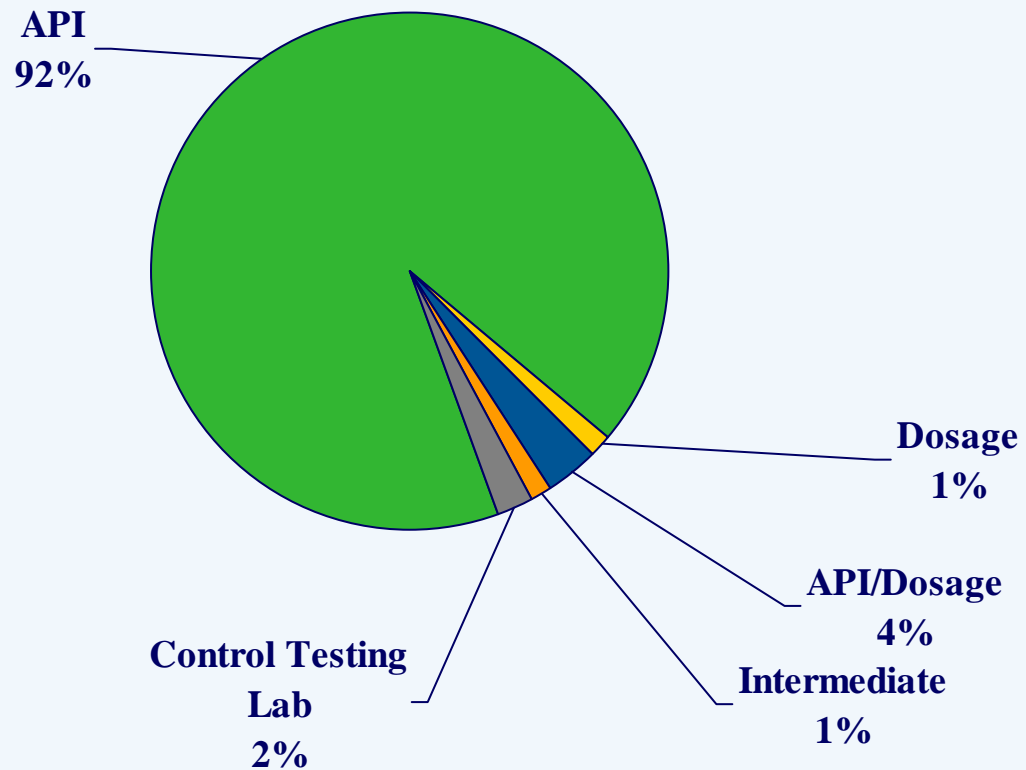
# China

- China's global reputation recently seriously damaged by a series of contamination incidents, some with fatal consequences.
- The result was extreme punitive action against corrupt officials and accelerated efforts to increase harmonisation of GMP standards with major regulators.
- GMP auditors being trained in MNCs in China and in the USA.
- Draft of new Chinese GMP Code for Pharmaceutical Products issued for comment October 2009

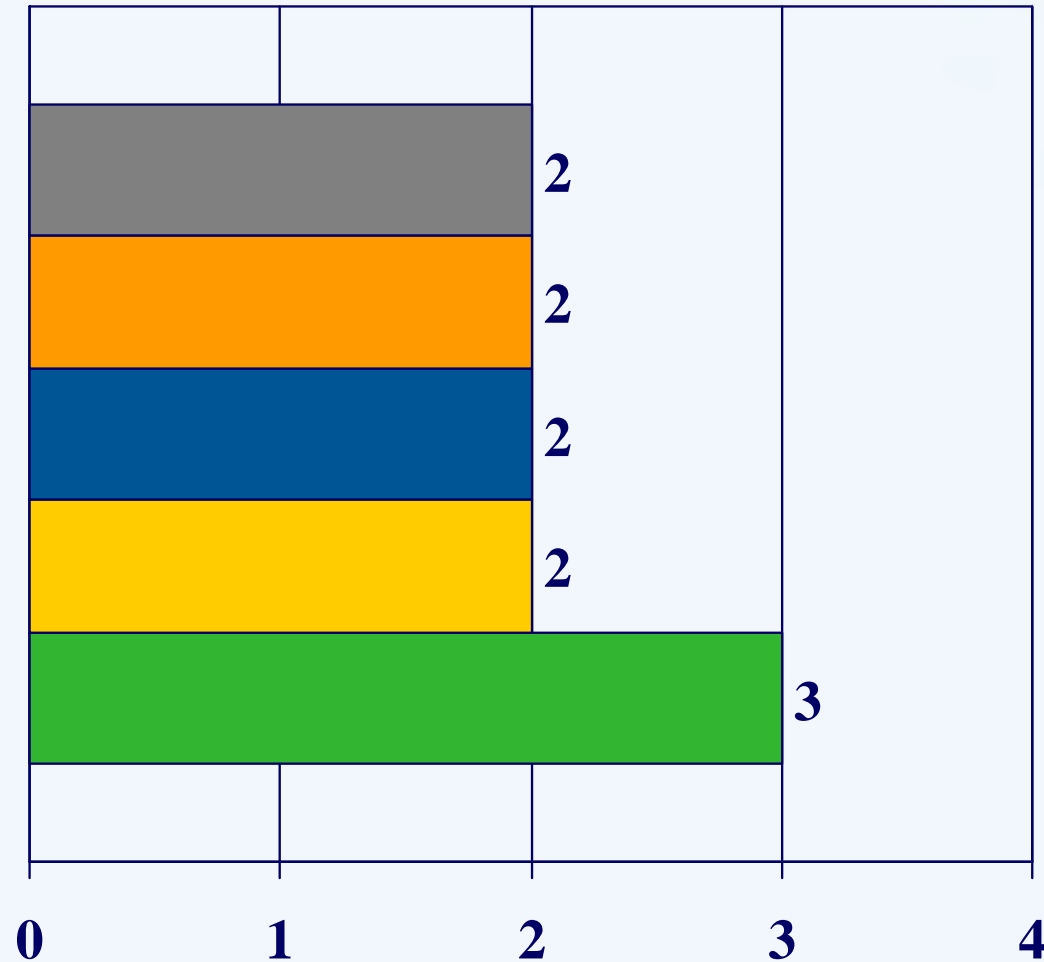
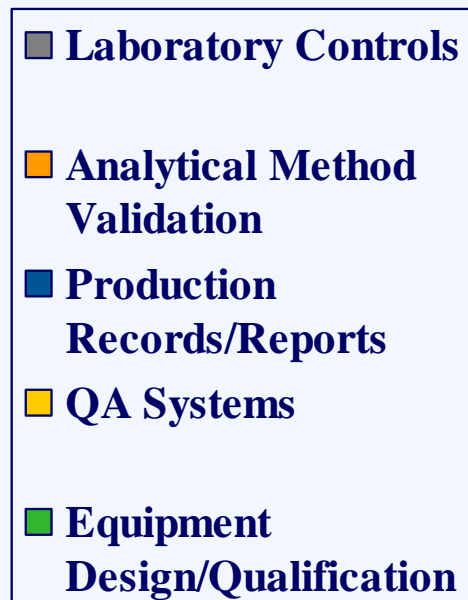
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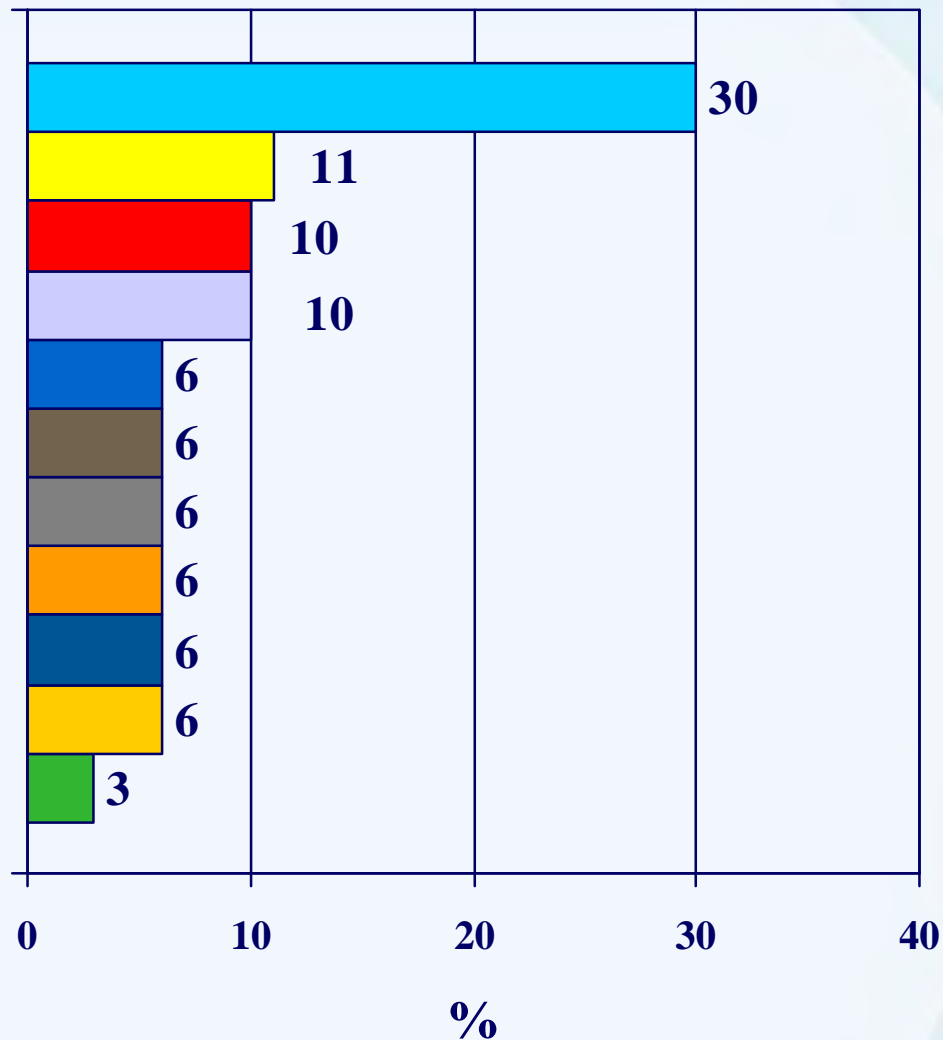
# Type of Manufacturing Facilities in China (FDA inspections 2004 -2007)



# US FDA Top Five GMP Deficiencies in China 2007



# US FDA Common GMP Deficiencies in China 2008



And now for the bad news - -

# Globalization and Compliance Issues

**Globalization of Drug Manufacture has led to an increase in compliance risks from less regulated markets**

- Less rigorous or different GMP standards
- Different IP rules

**What has been the impact on industry?**

More compromised products entering developed markets

- Generics manufacturers in third countries
- Outsourcing to third country contractors
- Third country raw material suppliers (APIs)
- Counterfeiters

**Due diligence & securing the supply chain are key**

# Globalization and Compliance Issues

## Supplier Quality Issues - Global Consequences

- **2007 DEG in tooth paste**
  - Tooth paste adulterated with DEG (substitute for glycerin)
  - Contaminant found in Chinese counterfeited products
  - Multiple recalls for DEG in tooth paste
  - Glycerin guidances issued and glycerin monographs updated
- **2008 OSCS in heparin**
  - Heparin drug substances adulterated with OSCS
  - Raw material sourced from China
  - Multiple recalls globally & multiple deaths in US
  - Global heparin monographs updated
- **2008 Melamine in infant formula**
  - Melamine adulterated infant formula
  - Chinese suppliers added to milk to increase nitrogen content
  - Resulted in infant deaths & illnesses in China
  - US issues Melamine Guidance

# DEG Contamination

- Problem: Recurrent DEG poisoning worldwide (resulting in hundreds of deaths)
  - 2006—Panama
  - 1995-1996—Haiti
  - 1990-1998—Argentina, Bangladesh, India, and Nigeria
- Cause: Diversion of industrial ‘glycerin’ for pharmaceutical use
- **FDA issued guidance in May 2007** to recommend testing and other controls to avoid DEG contamination:
  - Guidance for Industry: Testing of Glycerin for Diethylene Glycol*

# Globalization and Compliance Issues

## Examples of Drug Recalls/Alerts/Port Bans

- **UK MHRA Class II Drug Alerts Due to Indian Contract Manufacturer**
  - MHRA inspection of firm indicated this contract manufacturer did not meet European GMP standards
  - Drugs from 7 firms using this contract manufacturer impacted
- **US FDA Warnings & Product Port Ban for Indian Generic Manufacturer**
  - 2 sites issued FDA Warning Letters in 2008 for serious cGMP issues
  - 30 generic products banned from entering US ports
- **US FDA Class I & II Recalls Due to Chinese API Firm**
  - Adulteration of heparin API in China with oversulfated chondroitin sulfate (OCSC) linked to as many as 146 deaths in US
  - Multiple firms globally impacted by adulterated heparin API
- **Australia TGA Class I Recall for Chinese Herbal Product**
  - Herbal products contained analogue of tadalafil, a prescription only medicine which could increase risk for stroke/heart attack
  - Added 'Undeclared Ingredients' (not licence holder)

# 2008 Examples of GMP Issues Noted in US FDA Warning Letters for Indian Manufacturers

## ● Company A

- Quality Control Unit failed to ensure quality and purity specs
- Beta-lactam containment program (measures taken to control cross-contamination) appeared inadequate to prevent potential for cross-contamination of pharmaceuticals
- Inadequate batch production and control records
- Inadequate failure investigations
- Inadequate aseptic (sterile) processing operations

## Company B

- No assurance responsible individuals present to determine firm takes necessary steps under cGMP
- Inaccurate written records of cleaning and use of major equipment
  - No assurance performance of equipment cleaning double-checked
- Incomplete batch production and control records
- Inadequate procedures for the review and approval of production and control records for drug products

# 2009 WHO Issues Warnings (Notices of Concern) to Indian Firms

## ● **Company X Cited for GMP**

- Inadequate documented evidence of process validation to include source data for quality control and analytical test results
- Possible cross-contamination and failure to exercise sufficient control over some materials

## ● **Company Y Cited for GMP**

- Concerns related to recoding of data and information in batch processing records and its control over the HVAC (heating, ventilation and air-conditioning ) system in some areas

## ● **Company Z Cited for GCP & GMP**

- Critical observations concern protection of trial subjects
- Discrepancies between electronic and paper versions of chromatograms

# 2009 Examples of GMP Issues Noted in US FDA Warning Letters for Chinese Manufacturers

## ● **Company C**

- Manufacture & laboratory testing of drug component was performed at 'Company D' (noted below) which was not identified on the Drug Master File (DMF)
- Fail to investigate discrepancies
- Contaminated product shipped to US (heparin contained OSCS)

## ● **Company D**

- Failure of Quality Unit to verify identity and purity of product
- Contaminated product shipped to 'Company C' (noted above)
- Lack adequate systems to ensure transferred manufacturing and testing procedures produce quality product
- Fail to conduct regular &/or annual Product Quality Review
- Fail to investigate discrepancies

# CEPs

- All 13 CEPs suspended or withdrawn by EDQM to July 2009 were in China and India

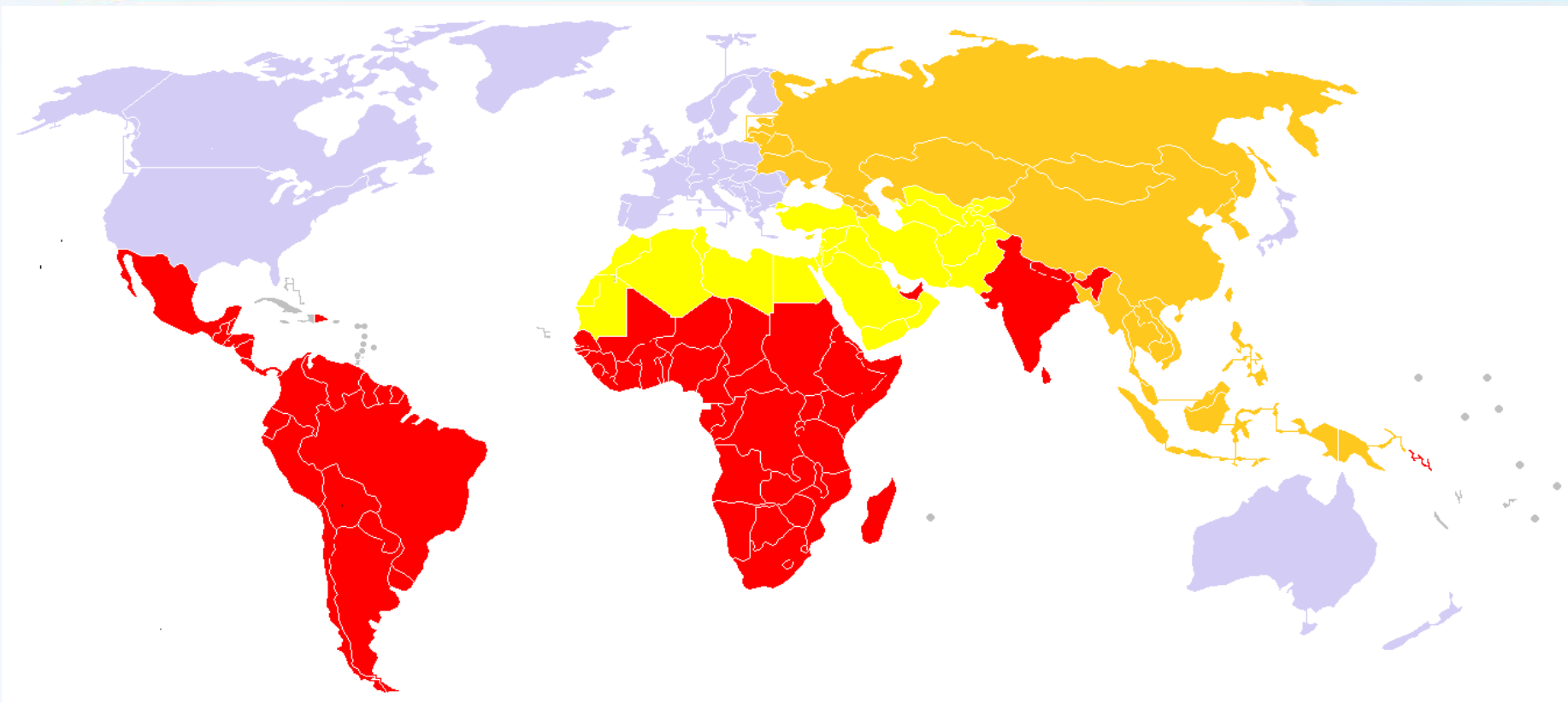
# Globalization and Compliance Issues

## What Happened Next?

- US initiates 'Importer Safety Bill' to increase resources for inspections and improve import practices
- EMEA, TGA & FDA collaborate to inspect API manufacturers
- FDA launches global supply chain pilot scheme
- APIC publishes 10 tips to audit suppliers
- Rx-360 Consortium initiated to ensure safety of Supply Chain
- China expressed commitment to improve GMPs and regulation
- China implements 'mandatory recall procedure'
- Industry initiates SFDA Inspector Training
- Japan MHLW to work with Asian countries to increase awareness
- FDA establishes inspection offices overseas via the 'Beyond Our Borders Initiative'; set up offices in India & China late 2008

# Counterfeits

# Global Scale of the Counterfeit Problem







**In 2007 4,08 million counterfeit medicines seized by EU customs**

*(Source: EU statistics – 19 May 2008)*

**About 50% of illegal Internet sales are counterfeits** *(Source: WHO – Nov 2006)*

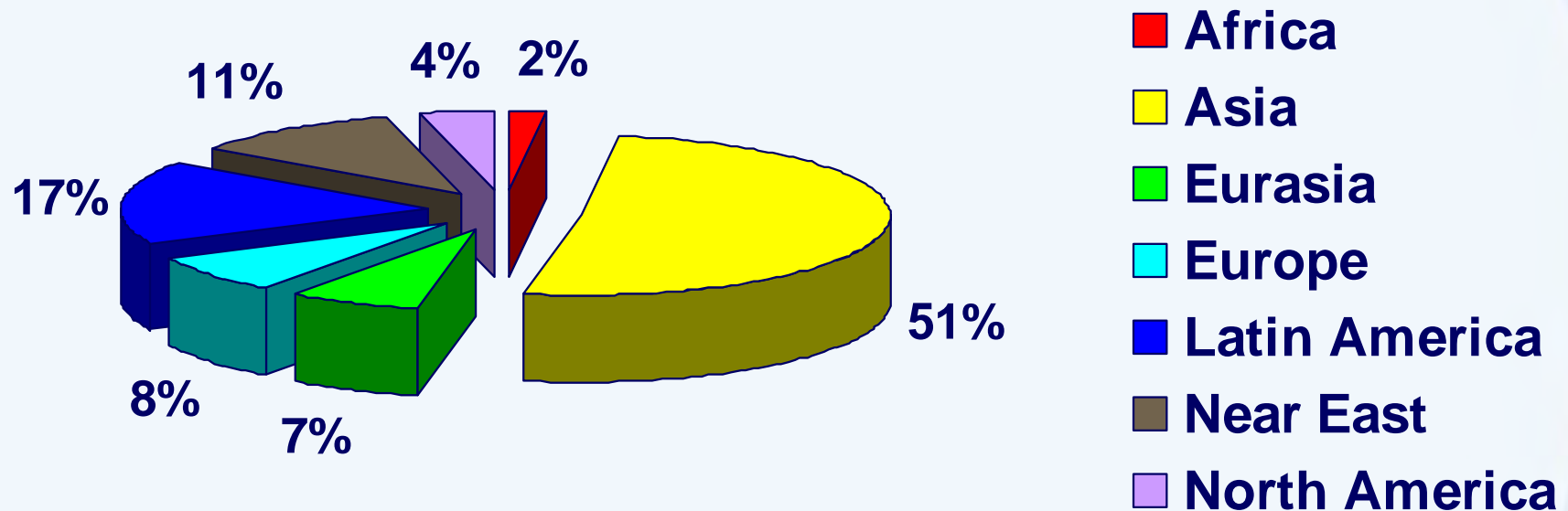
**Source: WHO - 2006**

	30% counterfeit
	20% counterfeit
	<10% counterfeit
	1% counterfeit

# Pharmaceutical Security Institute (PSI) Situation Reports 2006-2008

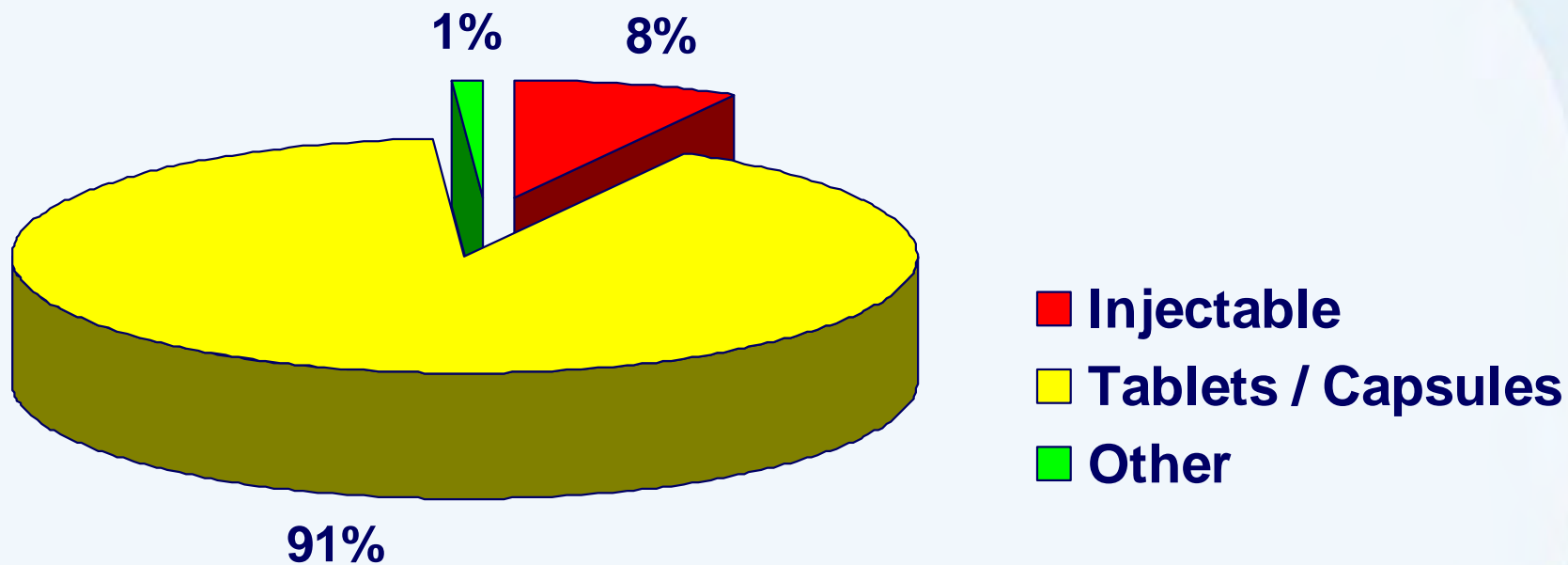
<b>PSI Situation Reports</b>	<b>2006</b>	<b>2007</b>	<b>2008</b>
Counterfeit incidents	1,152	1,513	1,834
Countries impacted	100	112	115
Different drugs involved	560	638	651
Law enforcement arrests	639	1,047	917

# Seizures of Counterfeit Product & Packaging by Region



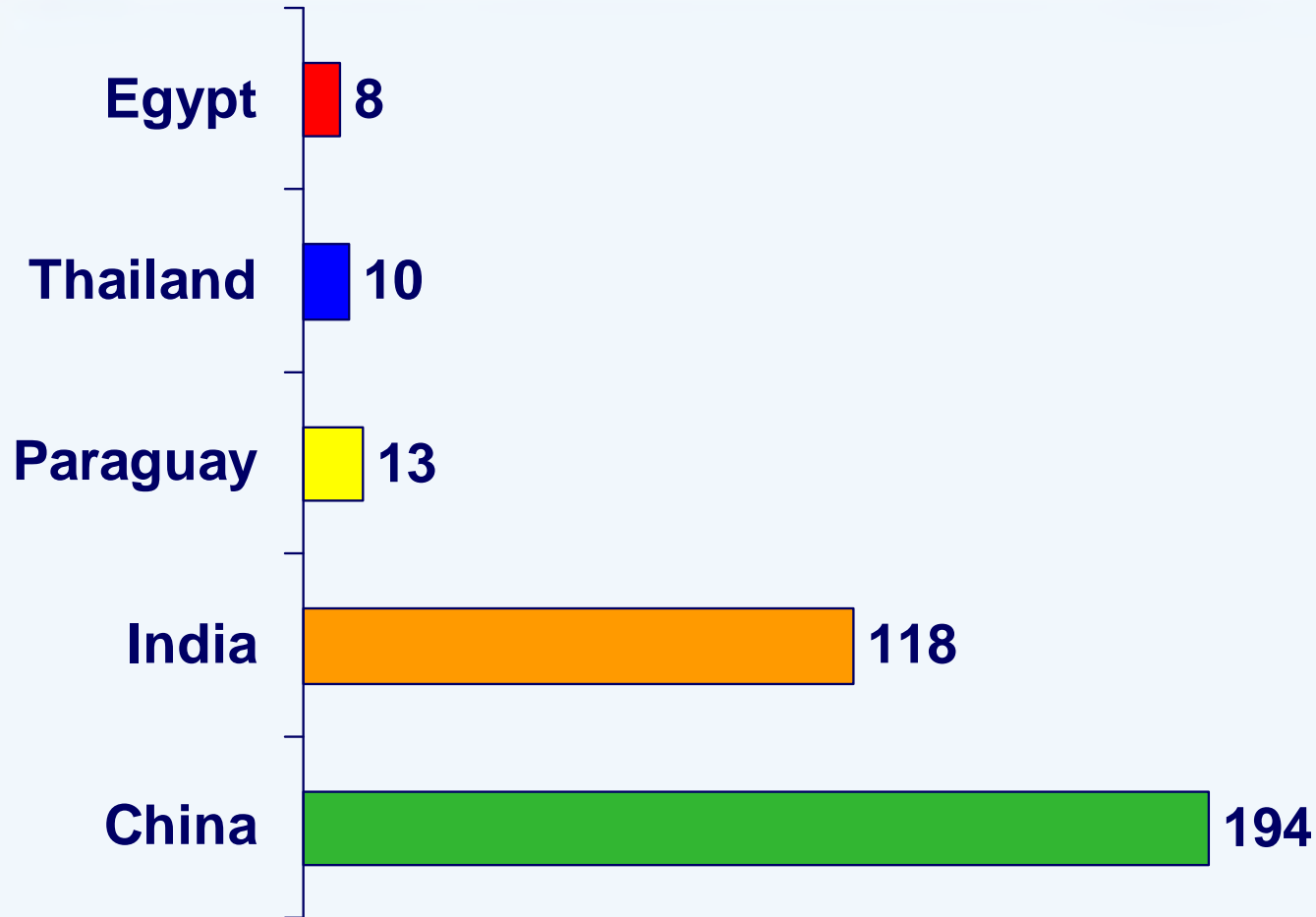
*(Source: Pharmaceutical Security Institute 2008 Situation Report)*

# Formulations of Counterfeit Medicines



*(Source: Pharmaceutical Security Institute 2008 Situation Report)*

# Counterfeit Products Origin 2008



*(Source: Pharmaceutical Security Institute 2008 Situation Report)*

# What can drug manufacturers do to prevent use of sub-standard pharmaceutical ingredients?

- Apply comprehensive approach to monitor ingredient supply chain integrity
  - Establish a robust supplier qualification program (e.g., audits, quality agreements, appropriate ongoing QC of incoming lots)
  - Only do business with trustworthy sources
  - Verify each ingredient shipment comes from approved suppliers/manufacturers
  - Verify shipments came through expected routes and were not diverted or tampered with

# Further insights

## China

- Major challenge for MNCs is stability & sustainability (knowledge plus desire to learn more > deep understanding > consistent, long term execution).
- Turnover is high. Local companies pay a lot for MNC- trained Quality professionals.
- Family separation (spouse, child, parents) is highly significant in Chinese culture and is a significant destabilising factor.
- The 'autocratic' leadership style still appears to be the most common in generating short term results, a challenge to the 'sustainability' issue.

# Further insights

## India

- Turnover of Quality professionals is a challenge, but not as bad as in China.
- 'Export only' businesses, with their higher margins, pay for the best people.
- Traditional, hierarchical management is very common and is a barrier to the effectiveness of emerging, highly educated talent.

# What does all this mean for the QP ?

- Know the manufacturer (ensure due diligence). The vast majority of India & China DP suppliers to Europe are good – but you need to be able to detect the others.
- Keep tabs on management structure, leaders and key personnel – things can change quickly. Establish good local contacts.
- For APIs, make sure you see audit reports (70% of APIs used in Europe now come from Asia).
- Watch for news on CEP suspensions (the joint FDA/TGA/EU/EDQM joint inspection initiative will lead to a sharp increase in the number of API inspections and potentially more CEP suspensions).
- Know the supply chain – infiltration of counterfeits into mainstream EU supply is unlikely, but possible.

# The rewards of investment



**Thank You.**

**Questions ?**