

# Rogue APIs The Ticking Bomb

**Guy Villax**

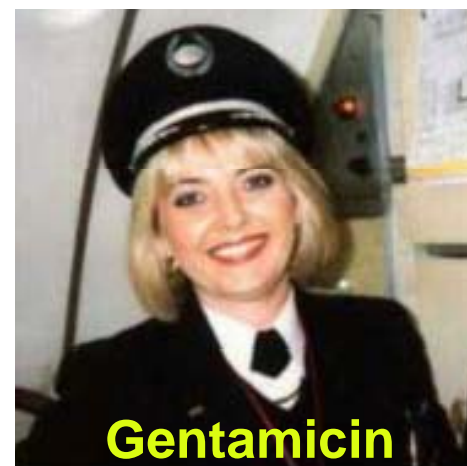
**Board member of EFCG and of RX-360**

**Hovione CEO**

## Agenda

- **The issue: Globalization & Hyper-competition**
- **Case Study: Heparin**
- **The root cause: Greed**
- **The solution: Regulators / Industry**

## Victims of falsified, imported pharmaceutical ingredients



## The Issue

- **In 25 years the Pharma industry went from:**
  - **A profitable, exclusively branded, mostly innovator business, essentially national in scope and vertically integrated – in the West**
  - **A mostly generic (70% of Rx), intensely globalised industry, with a supply chain of distinct players highly fragmented and specialized in their activities and often operating in a hypercompetitive commodity environment – de-localized to Asia**
- **The Regulators evolved to oversee a progressing science, but their oversight role infrastructure remained unchanged, and is today obsolete and unable to supervise this globalised industry**

## The Issue

- **A generic version is sold, and substitution permitted, because bioequivalence has been shown**
  - **GMP is expected to assure continued bioequivalence, but this is seldom ever re-verified**
  - **And over 20 years many changes take place... no-one updates their file unless forced to...**
- **The ticking bomb:**
  - **GMP is expensive,**
  - **Emergence of Asia, heterogeneous values and laws**
  - **Hyper competition and absence of enforcement makes short-cuts tempting and rewarding**

# Where are Unsafe APIs coming from?

**1 API batch = 10.000s to 100.000s of patients**



## Safety of the Supply Chain of APIs in and from China

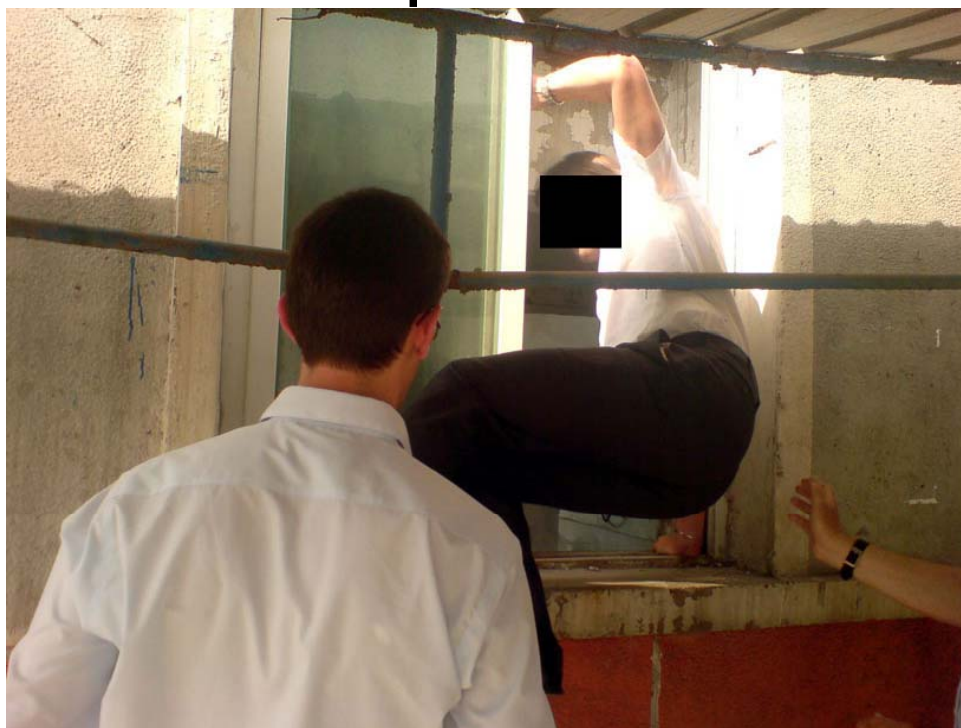


**Empty drums concealing  
a vast warehouse of  
falsified ‘chemical-grade’  
APIs and intermediates in  
a ‘pharmaceutical’ API  
plant exporting to  
Europe.**

*(Zhejiang, China, 2008)*

# Can audits waive the need for systematic inspections?

## What inspectors can do:



Force their way into a concealed workshop  
through its window

(At an API plant in Liaoning, China, 2008)

## What auditors are told:

*"I am sorry, if you require  
to audit the para-  
aminophenol plant, we  
will refuse the audit"*

(A paracetamol manufacturer  
in Zhejiang, China, 2009)





# The Heparin tragedy



Why this presentation ?



## Business of Counterfeit Heparin and its implications

Guy Villax  
Member of the EFCG Board  
Head of the Globalization Task-Force

3rd EFCG Pharma Business Conference  
29/30th May, 2008  
Lisbon, Portugal

- Almost 100 deaths have been traced to counterfeit heparin, probably a better data collection system would establish that many hundreds are now dead – not because of a regulatory failure but because of greed. Crime has been committed with premeditation and with recourse to science and industrial means – and nobody spells it out.
- Did someone make millions in profit, and poisoned to death hundreds of weak, defenseless patients ?
- Is a police investigation underway ?
- Penny wise, pound foolish – these events cost / will cost billions to several big companies – and damaged brands.

[efcg.cefic.org](http://efcg.cefic.org)

To access the complete document presented at  
the 2008 Lisbon EFCG Business Conference  
please visit

[http://efcg.cefic.org/isoFILES/publications/items/DOWNLOAD\\_181.pdf](http://efcg.cefic.org/isoFILES/publications/items/DOWNLOAD_181.pdf)

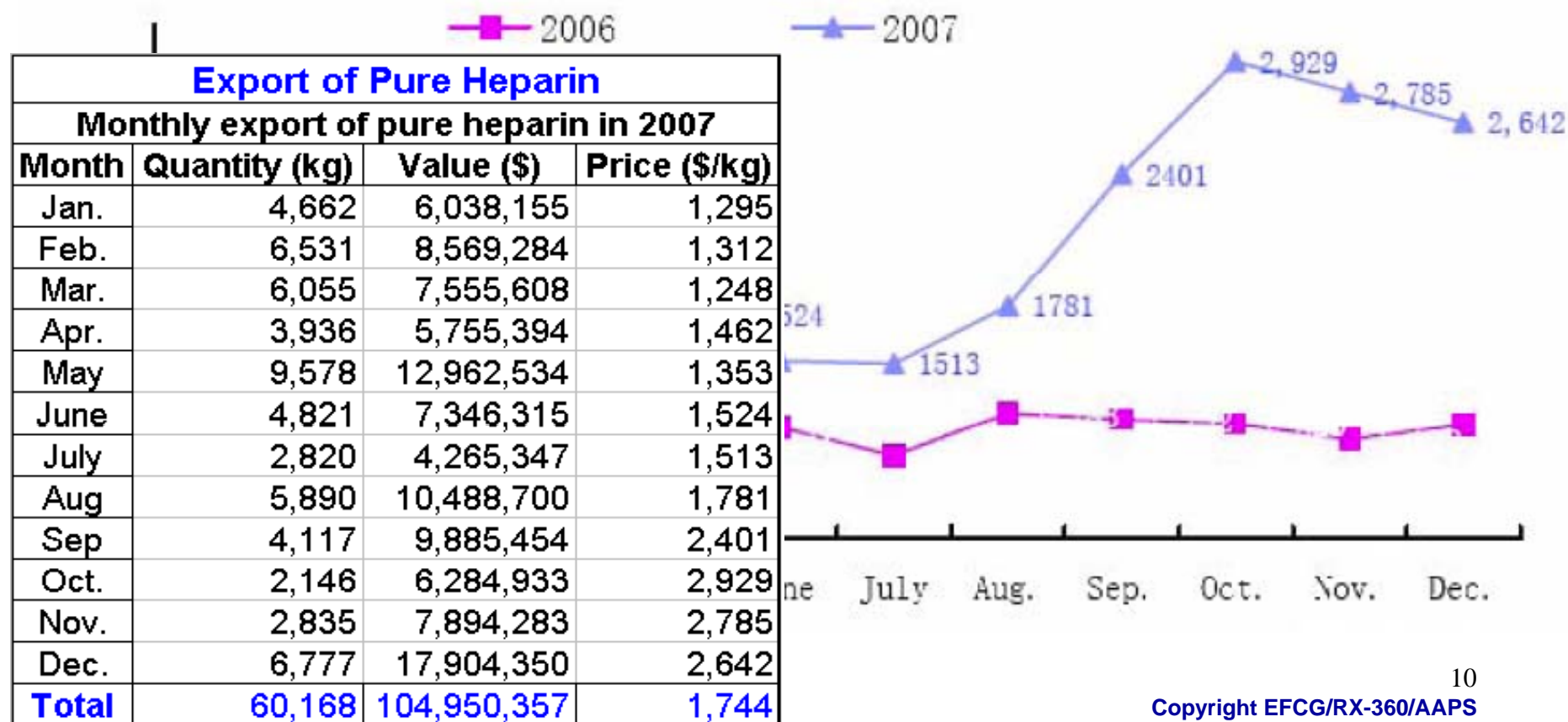
For all relevant material please visit

<http://efcg.cefic.org/publications/items/2008-05.html>

# August 2007: A Flag for all to see: PRC Export & Price of Pure Heparin

Unit: \$/Kg

Graph 4 Monthly Export Prices Trend (2006's vs. 2007's)



## Exporters stats of pure heparin in 2007

Rank	Exporter	Quantity (Kg)	Value (\$)	Quantity (%)	Price (\$/Kg)
1	Shenzhen Hepalink Pharmaceutical Co.,Ltd.	17,198	27,565,212	28.58%	1,603
2	Changzhou Qianhong Bio-Pharma Co., Ltd	10,011	18,155,545	16.64%	1,814
3	Yinan Dongyuan Bioengineering Co.,Ltd	6,602	11,542,480	10.97%	1,748
4	Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd	6,187	10,171,737	10.28%	1,644
5	Shen Zhen Spread Import & Export Trade Co., Ltd.	5,375	12,109,989	8.93%	2,253
6	Chongqing Imperial Bio-Chem.Co., Ltd.	4,205	6,030,315	6.99%	1,434
7	Changzhou Kaipu Biochemistry Co.Ltd.	3,518	6,370,910	5.85%	1,811
8	Shanghai No. 1 Biochemical & Pharmaceutical Co.	3,390	6,920,091	5.63%	2,041
9	Shanghai Biofine International Co., Ltd.	1,107	1,877,750	1.84%	1,696
10	Hebei Changshan Biochemical Pharmaceutical Co., Ltd.	1,024	1,769,238	1.70%	1,728
11	Dongying Tiandong Biochemical Industry Co., Ltd	471	627,370	0.78%	1,332
12	China Jiangsu Medicines And Health Products Imp.	155	157,207	0.26%	1,014
13		148	207,220	0.25%	1,400
14		140	322,612	0.23%	2,304
15		138	228,614	0.23%	1,657
16		100	95,000	0.17%	950
17		92	267,264	0.15%	2,905
18		91	169,296	0.15%	1,860
19		72	113,529	0.12%	1,577
20		50	109,200	0.08%	2,184
21	SHANGHAI SYNNAD CHEMICAL CO., LTD.	37	40,300	0.06%	1,089
22	Liaoning Pharmaceutical Foreign Trade Corporation	22	39,166	0.04%	1,780
23	Jiangsu Guotai International Group Huatai Imp. & Exp.	12	15,240	0.02%	1,270
24	Shenzhen Techdow Pharmaceutical Co., Ltd	11	25,033	0.02%	2,276
25	NanchangLifengIndustryAndTradingCo.,Ltd	5	7,200	0.01%	1,440
26	China Jiangsu International Economic-Technical	3	4,260	0.00%	1,420
27	Argosi International Co., Ltd.	2	4,890	0.00%	2,445
28	Liaoning Chemical Industry Import And Export	1	1,545	0.00%	1,545
29	Sichuan Sun-Rise Health Products Co., Ltd.	1	2,144	0.00%	2,144
	Total	60,168	104,950,357	100.00%	1,744

### Pure Heparin PRC exporters

- 10 producers make 97%
  - Wide price fluctuation
- Producers >< Exporters

## Exporter percentage of Destination Countries in 2007

		Quantity (Kg)	Value (\$)	Quantity (%)	Price (\$/kg)
1	Germany	13,794	24,958,119	22.93%	1,809
2	USA	13,006	25,266,600	21.62%	1,943
3	France	10,645	12,499,915	17.69%	1,174
4	Italy	8,252	16,370,393	13.72%	1,984
5	Austria	5,094	9,673,498	8.47%	1,899
6	Singapore	3,363	6,669,851	5.59%	1,983
7	Danmark	1,125	1,404,194	1.87%	1,248

**US, Germany, France, Italy, Denmark, Switzerland, Sweden and Japan have all pulled Heparin products from the market due to the presence of contamination or as a precautionary measure after API links to China were made.**

**TGA website: Contamination in samples of Heparin distributed in Australia.**

24	Arab Emirates	53	164,729	0.09%	3,108
25	Yugoslavia	36	22,413	0.06%	623
26	Pe				
27	Ja				
28	Ro				
29	So				
30	Me				
31	Li				
32	UK				
33	Sw				
34	Ni				
35	Ar				
36	Ho				
37	Cz				
38	No				
39	Co				
	To				

### 2007 PRC Pure Heparin exports

- 39 countries
- Data seems low: 60 ton, US\$105m, \$1744/kg
  - Maybe 100ton - \$200m
- Correlation with EU traders and producer locations.

# **Holders of EDQM-issued CEPs as of 16th May 2008**

Holder Name	City	Country	Certificate Number	Issue Date	Status	Type
Welding	Hamburg	D	R0-CEP 2003-192-Rev 00	22.06.2005	VALID	Chemistry
Helm	Hamburg	D	R0-CEP 2002-012-Rev 03	03.11.2005	VALID	Chemistry
Leo Pharma	Bellerup, DK	DK	R0-CEP 2001-446-Rev 01	19.11.2004	VALID	Chemistry
Wexport	Cork	IR	R0-CEP 2001-445-Rev 01	20.12.2004	VALID	Chemistry
Lab Derivati Organici	Milano	IT	R0-CEP 2004-165-Rev 00	16.01.2006	VALID	Chemistry
Opocrine	Corlo Di Formigine	IT	R0-CEP 2002-006-Rev 03	13.07.2006	VALID	Chemistry
Organon	Oss	NL	R0-CEP 2003-163-Rev 01	22.06.2007	VALID	Chemistry
Changzhou SPL	Changzhou City	PRC	R0-CEP 2004-080-Rev 00	03.08.2005	VALID	Chemistry
Nanjing King-Friend	Nanging	PRC	R0-CEP 2005-070-Rev 00	12.10.2006	VALID	Chemistry
Shenzhen Hepalink	Shenzhen	PRC	R0-CEP 2006-059-Rev 00	27.02.2008	VALID	Chemistry
Yantai Dongcheng	Yantai, Shandong	PRC	R0-CEP 2003-197-Rev 01	14.09.2007	VALID	Chemistry
SPL	Waunakee, WI	USA	R1-CEP 2001-243-Rev 00	30.11.2007	VALID	Chemistry
12						

<b>middlemen</b>
<b>Producers / Purifiers</b>
<b>likely purifiers</b>
<b>No view</b>

## Attempting to explain flows

Top	Exporter	Kg	%	In rounded tons						
				D	USA	F	IT	AU	Singpre	DK
1	Shenzhen Hepalink Pharmaceutical Co., Ltd.	17,198	28%	0.2	2.8	10	0.2	1.1	2.2	0
2	Changzhou Qianhong Bio-Pharma Co., Ltd	10,011	17%	6.6	0	0	1	2.3	0	0
3	Yinan Dongyuan Bioengineering Co.,	6,602	11%	5.2			0.2			
4	Nanjing King-Friend Biochemical Pharmaceutical Co., Ltd	6,187	10%	0	2.7	0.5	0	1.3	0	0
5	Shen Zhen Spread Import & Export Trade Co., Ltd.	5,375	9%	0	0	0	5.4	0	0	0
6	Chongqing Imperial Bio-Chem.Co., Ltd.	4,205	7%	0.9			0.6			1.2
7	Changzhou Kaipu Biochemistry Co.Ltd.	3,518	6%				0.4			
8	Shanghai No. 1 Biochemical & Pharmaceutical Co.	3,390	6%							
9	Shanghai Biofine International Co., Ltd.	1,107	2%							
10	Hebei Changshan Biochemical Pharmaceutical Co., Ltd.	1,024	2%							
	others	2,001	3%							
		60,618	100%							

**Genuine producer holding a CEP**

**Would Helm be their agent and hold "their" CEP**

**Would Welding be their agent and hold "their" CEP**

**Could Changzhou SPL exports not be listed here ?**

**Export patterns mirror:**

- Dependence on middle-men
- Big-pharma client (close relationship)



## Complex supply chain

- 1 injection = 1 pig
- 1 Kg of Crude Heparin needs intestines from ~3000 pigs
- 1 Kg of Purified Heparin needs intestines from ~4500 pigs
  - 100 tons of heparin = ~300 million pigs
- Mr. Yuan's small factory makes 6Kg a month,
  - Sells for \$900/kg
  - \$10.000/year
- Mr. Wang's Anhui plant is larger:
  - 6000 pigs/day or 1 ton/year
  - \$1m/year
- QC: sample is taken and tested: stops sheep's blood clotting?
- Crude workshops make 1-2Kg month; 25kg/year; Pareto tells us that 20 tons are made by 1000 workshops; with 80% 80 tons done by 50 larger plants – this is complex
- A wonderful opportunity for brokers, traders and consolidators that will sell to the GMP purifiers.

## Costs and Prices

- **Shortage and Dependence on China:**
  - Since mid-2006 China's pig herds have suffered serious outbreaks of porcine reproductive and respiratory syndrome – viral illness commonly known as blue-ear disease
  - Over the same period feed prices went up in China, breeding of Chinese pigs dropped
  - Heparin demand continues to grow worldwide
  - EU based extraction and purification capacity have reduced in the last 10 years, (only 3 EU extractors remain) – hence significant PRC dependence
- FDA said on 22 April 08 “Contaminated batches were found from as early as 2006” “but a spike of illnesses began in November 07 and persisted through February 08”
- During the summer of 2007 prices start to increase
  - Crude Heparin     \$600 to \$1500/kg
  - Pure Heparin     \$1200 to \$2700/kg
- Prices of non-Chinese Heparin are 20 to 30% higher than Chinese prices; some industry experts say 20-30% is an underestimation.

## Bad Science ?

- A polysaccharide over-sulfation is described in WO/2005/058976 by treating in DMF with pyridine-SO<sub>3</sub> complex, (18h 45°C) followed by neutralization with sodium hydroxide and precipitation in acetone saturated with sodium chloride. The obtained crude product contains lots of salts and shall be subject to diafiltration and/or resin treatments and then isolated by lyophilization
- Baxter has several patents on chondroitin as additive (dialysis mentioned)
- Some of the heparin producers are also chondroitin sulfate producers...

## Crime ... ?

- **Chondroitin Sulfate quoted in 2008 at USD53/kg for 1000Kg**
- **OSCS was the result of molecular design**
- **OSCS was designed to go unnoticed in routine QC testing**
- **OSCS does not occur in nature nor has existing, legal applications: Was synthesized for this particular purpose**
- **If 4 to 12 months 33% of exports had an average of 10% contamination:**
  - **Low end 1 ton of OSCS**
  - **High end 3 tons of OSCS**
    - **Profit of \$1m to \$3m**

# Chinese Heparin Supply Chain (reality)

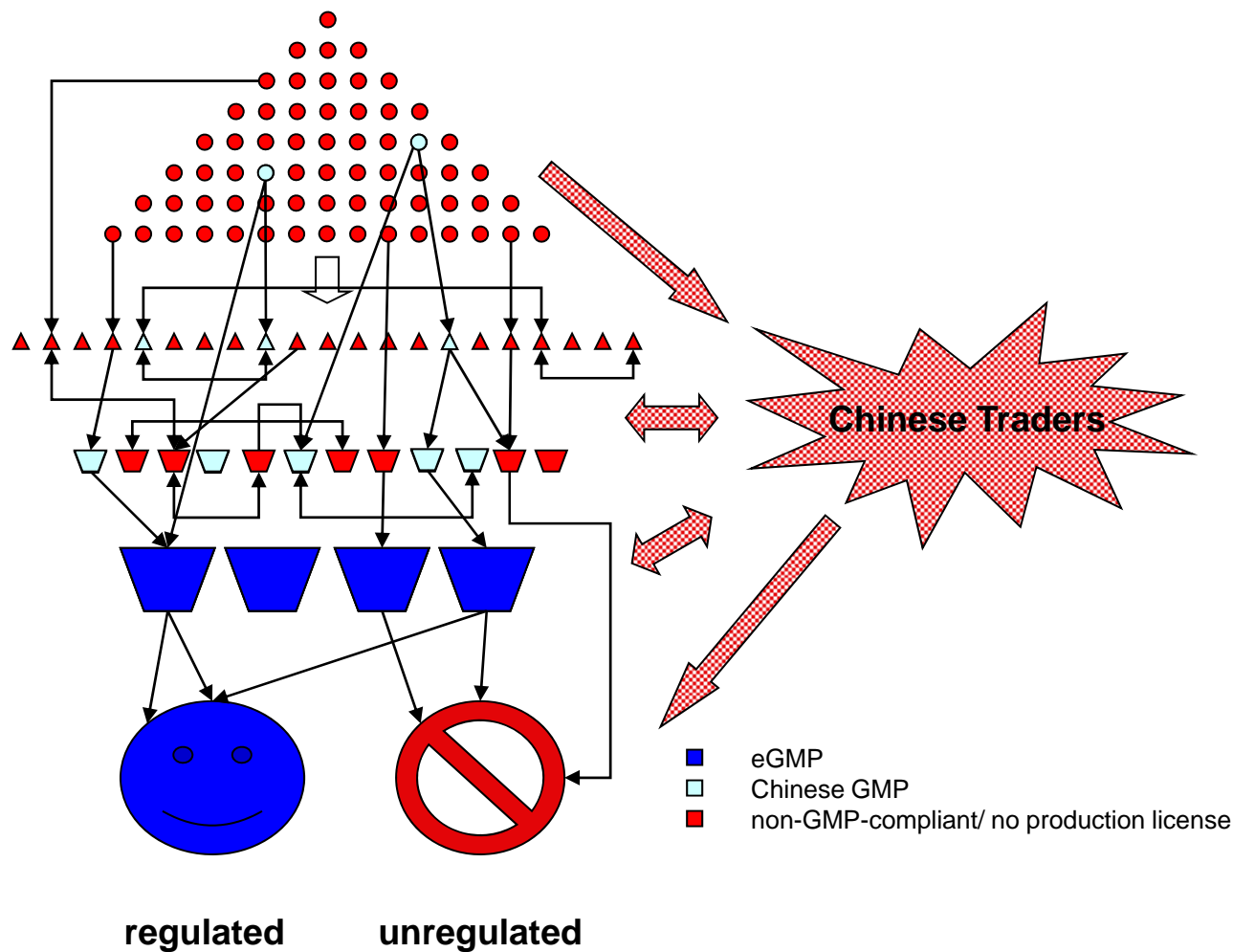
crude Heparin workshops

small purifiers

medium purifiers

big purifiers

markets



# Chinese Heparin Supply Chain (crime hypothesis)

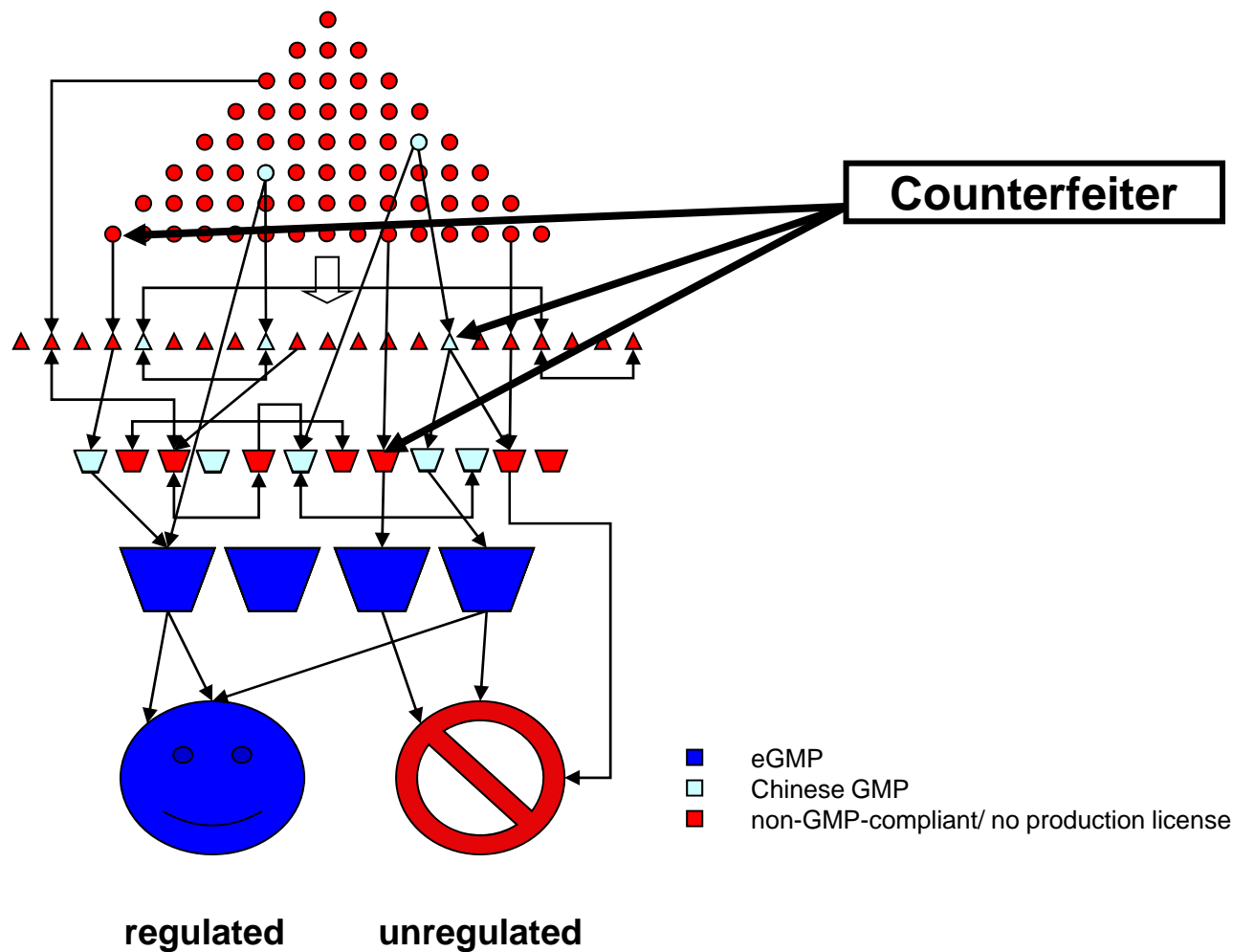
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# Chinese Heparin Supply Chain (crime hypothesis)

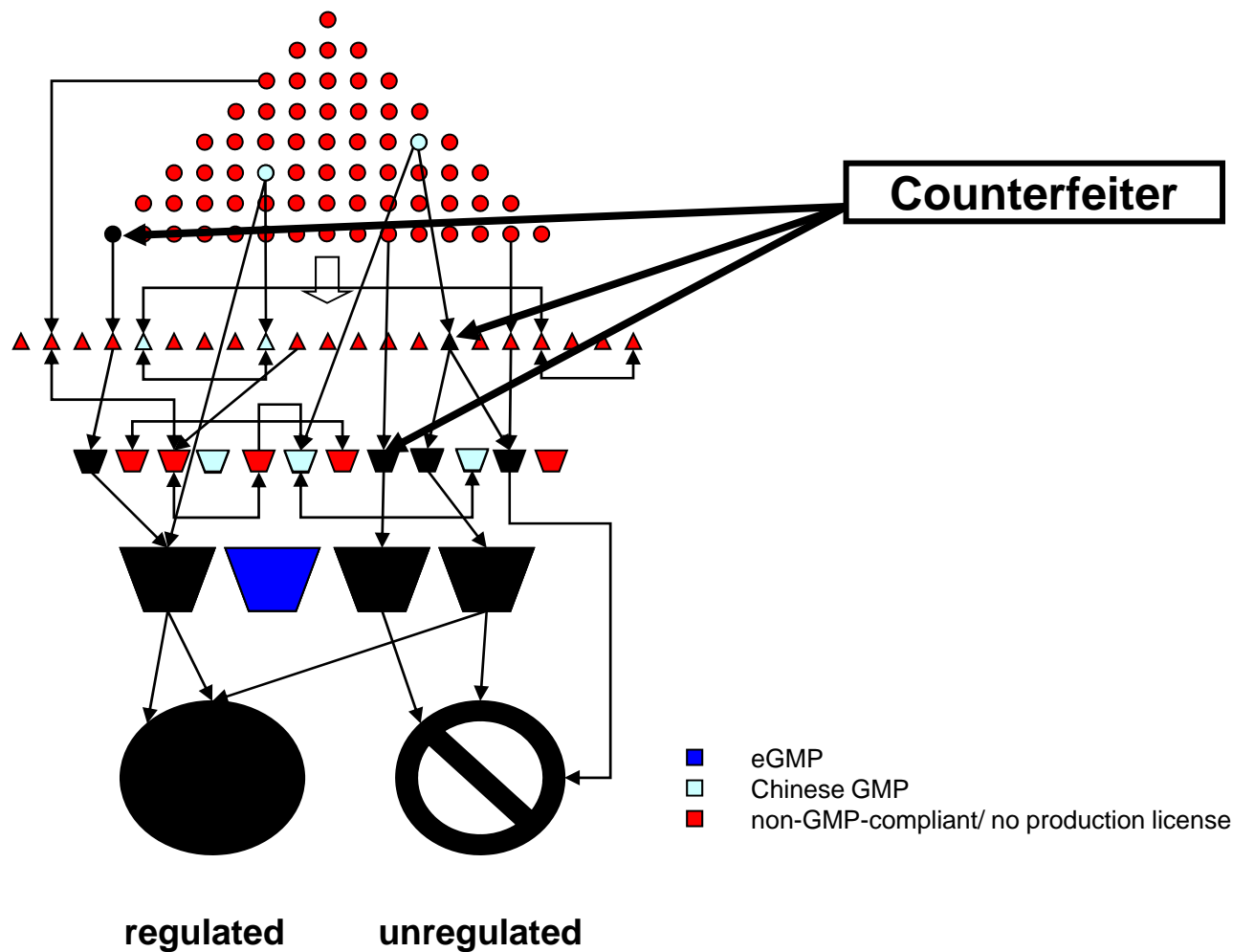
crude Heparin workshops

small purifiers

medium purifiers

big purifiers

markets



## And when you thought it was now safe...

- Monday, May 11, 2009
- [Chinese Heparin Producers Get Warning Over Falsified Information](#)
- ***FDA issues letters to two more Chinese manufacturers regarding tainted Heparin***

It reads like a bad sequel as more companies have been named in the tainted heparin scandal...

Two Chinese companies have been issued warnings from the FDA for falsifying information on Heparin. Shanghai No. 1 Biochemical & Pharmaceutical said they were manufacturing heparin, when in fact they were purchasing it from two outside companies. One supplier is no longer producing the medicinal product.

- <http://securepharmachain.blogspot.com/2009/05/chinese-heparin-producers-gets-warning.html>

Secure Pharma Chain Blog - Promoting Peace of Mind in the Global Supply Chain

## Crystal Clear

<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm136668.htm>

- The inspection revealed that the facility was not manufacturing, and did not appear to have ever manufactured, Heparin Sodium USP (or heparin sodium) for the U.S. market.
- ...manufacturing of heparin sodium was conducted at facilities other than the one identified in your DMF.
- ... :uncovered untrue statements and information submitted by your firm to the agency with respect to the actual manufacturer(s) of heparin sodium.

## The Solution – Part I





- 1. Developed countries have ICH Q7a in their law**
- 2. Few countries consider fake medicines to be a more serious offense than a fake Lacoste®**
- 3. Few countries license pharma products importers and limit trading**
- 4. Few countries link API importation OK to Medicine Agency OK**
- 5. Few countries treat exports same as local supply**
- 6. No country imposes a recall (or any action) by MAH when a counterfeit of its medicine is identified**



## Registration process of makers of imported API:

- **Importer registration pre-approval process: identifies maker and importer of API, is non-transferable, is a lengthy and demanding process**
- **Manufacturing site must be registered and unambiguous data must be provided**
- **Local agent is liable**
  - **USA: YES ~3500 filed a foreign establishment registration**
  - **EU: No, registration not required**
  - **Japan: YES ~2000 foreign accredited firms + import license**
  - **China: YES - Expensive Import license registration**





- **Foreign inspections – grow in number and data pooled:**
  - **USA** ca. 250/year of which ca. 80 on APIs, doubling as from 2009
  - **EU** Excluding “centralized” products: ca. 60/year, most initiated and coordinated by EDQM (= non-EU), coordination between member states in its infancy
  - **Japan** ca. 120/year 50:50 API/Formulations
- **Except for FDA, inspections do not include a focus on Fraud**
- **Other checks:**
  - **Cross checking batch numbers between API producer and API user**
  - **Sampling and testing at the border**
  - **Forensic finger-printing of APIs**



**USA: Stiff penalties. You go to jail, e.g.. back-dating is fraud, FOI enables active “name and shame” process**

**EU:**

- **EFCG’s 2006 questionnaire evidenced virtual absence of sanctions (recalls, fines, jailings) => deterrence was nil**
- **as from 2008 things started to change:**
  - **Recalls**
  - **CEP suspended as a result of inspections**
  - **API users switching back to old suppliers (after 10 years’ of absence)**

**Japan**

- **??**

## What deterrence do we need ?

- **Sanctions that hurt the business and cost more than the savings / profits of non-compliance:**
  - **Recalls and Fines**
  - **Withdrawal of the Marketing Authorizations**
- **Sanctions that affect the brand of the offender:**
  - **“Name and Shame” - make the sanction and the cause of the sanction transparent to the public, and accessible, EUDRA-GMP database; EDQM website**
- **Sanction on individuals that bite – e.g. “de-barred” convictions – causing a professional to no longer be employable in the pharma industry**

## Why don't Regulators address repeat offenders ?

- **Asian API producers**
  - Caught, suspended
  - Re-apply – approved
  - Caught, suspended
  - Etc..
- **Traders/Agents**
  - Free-ride on Europe's reputation and values
  - Involved in several of the tragedies (Haiti, Panama, Heparin, Gentamicin)
  - Traders are holders of EDQM CEPs (with a dramatically higher incidence of CEP suspensions and withdrawals by EDQM, and FDA warning letters from FDA)
  - Take a key role in the business of approved registration dossiers of generics and control API supply chains. In certain EU countries traders have a 50% market share in generic dossiers !

## Ticking Bomb

- **EDQM risk-based inspectional approach led to 60 CEP suspensions, all in Asia:**
  - **Suspended CEPs supported marketing authorizations that allowed medicines in the market for many years... sub-standard medicines, unknown health impact**
  - **EDQM inspects only a fraction of all CEP holders**
- **Gentamicin / Heparin / Glycerin...**
  - **Acute toxicity issues trigger immediate action**
  - **What if toxicity is long-term only ?**

## The Solution – Part II

**Industry also has a role to play, not just the Regulators.**

- **Penny wise, pound foolish**
  - Pure Heparin from China costs      \$2500/kg
  - Heparin formulations retail at:      \$100.000 for one kg
- **Did Purchasing not see the red flag in August 2007 ?**
  - **Where were the QPs, QA ? Where was the CEO that said Finance could not over-rule QA?**
- **149 deaths, brands damaged, likely damages in the millions**

**Rx-360 – industry voluntary group collaborating to make the pharma supply chain secure and authentic**

**CEOs to take a fresh look at the balance of power between the Quality Unit and Finance/Purchasing.**



TS



**NEIGHBOURS** Borut Pahor (left) and Anka Kosor (right), the prime ministers of Slovenia and Croatia, sign an arbitration agreement on a long-running border dispute, mediated by Fredrik Reinfeldt, Sweden's prime minister (centre), in Stockholm. Last month, Slovenia ended its ten-month block on Croatia's membership talks with the EU.

## The paper clip

### Daily press review

#### Economic balancing act **EV+**

It won't be easy, but developed countries must take steps to rebalance the global economy in order to achieve growth.

Michael Spence

May, 5 November 2009

#### Are you ready to be carbon-neutral **EV+**

China is making ambitious pledges to cut and offset

#### The e-paper (for subscribers only)



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Carbon-neutral



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**14Oct09: Financial Times reported: Chirac demands tough action on fake medicines. He says: “Fake medicines have become a real market that is poised to overtake that of narcotics... An international convention ratified by the UN will provide a framework to attack criminal networks.”**

**Thank you.**  
**For more information, please contact:**

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**For more information visit:**

**<http://efcg.cefic.org/publications/items/2008-05.html>**