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Business of Counterfeit Heparin and its implications

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

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Why this presentation ?

- 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.

Why this presentation ?

- This presentation does not represent the views of EFCG, the responsibility is entirely mine.
- I am not an expert in Heparin, this is based on fact and data believed to be correct from reputable press. It includes educated guesses from over 20 years of exprience in APIs, China and working with traders. This presentations was offered for review and comments to several people far more expert than me in the heparin business.
- If you feel there are inaccuracies, or if you have better data, please advise so we may revise this presentation

Agenda

- The Worlds of Heparin: Photos, numbers and flows
- August 2007 – a Flag for all to see
- How much profit ?
- Heparin 2008: re-cap
- USA vs. Europe
- Conclusions
- Next Steps

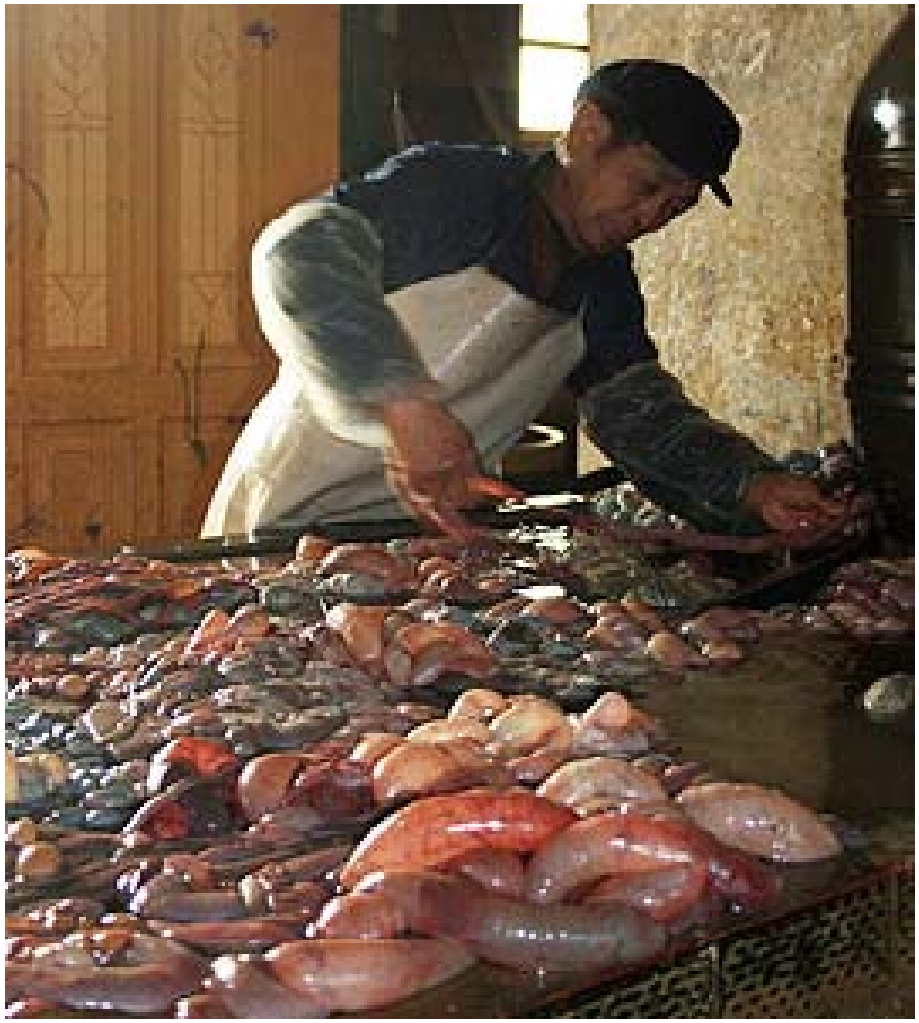
The Worlds of Heparin: Photos, numbers and flows

- Press Photos
  - New York Times, Washington Post and Wall Street Journal
- Numbers
  - World pig population
  - PRC heparin exports data
  - Cost of production, sales price
- Flow of product
  - Global flows
  - Examples

Where a Drug Begins

- The first steps to produce crude heparin, the main ingredient in an anti-clotting medicine, often take place in small factories across China -- many of them primitive.
- Above, bare-handed workers at Yuan Intestine & Casing Factory, in a small farming village in Shandong province, untangle and flush pig intestines that will be used to make the medication (WSJ 21Feb08).

Where a Drug Begins



- The men wring pulp from pig intestines and heat it in open cement vats.
- After further processing by more sophisticated plants, the chemical is made into intravenous drugs given to patients around the world having surgery or patients who need kidney dialysis or blood transfusions (WSJ 21Feb08).

Where a Drug Begins

- The process for getting raw heparin is rather simple. First, the company picks up barrels of pig intestines from slaughterhouses (WSJ 21Feb08).

Where a Drug Begins

- **Workers use a machine to wring the pulp from the inside of the intestines. (WSJ 21Feb08)**

Where a Drug Begins

- An ion-exchange resin is used to extract the heparin from the pulp, and the resin and heparin are bathed with salt water and stirred (WSJ 21Feb08).

Where a Drug Begins

- Then the resin is filtered away, leaving a solution of heparin and salt water. Finally, alcohol is added to separate the heparin from the salt water. The alcohol mixture is stored in earthenware jars covered with gunnysacks.
- After the insides are removed, outer layers of intestines -- visible at the rear draped over the lips of barrels – are ready to be used as sausage casings (WSJ 21Feb08).

Where a Drug Begins

- Above, a worker shows crude heparin, stored in a plastic bucket (WSJ 21Feb08).

Where a Drug Begins

- Extracting chemicals from animal tissue is by its nature a messy business. U.S. and European drug makers stopped relying on cows -- once widely employed as a source of heparin -- after the discovery of mad-cow disease, fearing that the illness could be passed on (WSJ 21Feb08).

Where a Drug Begins

- Since mid-2006, China's pig herds have suffered serious outbreaks of porcine reproductive and respiratory syndrome. In theory, sick animals are supposed to be rejected, but in practice, enforcement can sometimes be lax (WSJ 21Feb08).

Where a Drug Begins

- After it is dried, the crude heparin goes through many steps aimed at ridding it of harmful substances before it ends up in medications.
- The lack of consistent oversight of China's heparin industry highlights the regulatory gaps as pharmaceutical companies become increasingly global in their purchase of ingredients (WSJ 21Feb08).

Where a Drug Begins

- Yet there is so much demand that heparin traders are recruiting people to make the chemical. A company offering training programs for farmers advertised that annual profit could reach $20,000 -- a fortune in rural China (WSJ 21Feb08).

Where a Drug Begins

- Amid the strong market for heparin, Huai Ning Xue Lian Livestock Product Co., based in the eastern province of Anhui, opened a large, more modern heparin plant in November.
- There, workers in rubber boots and thick aprons process the intestines on three assembly lines (WSJ 21Feb08).

Where a Drug Begins

- Wang Jiewen, the company owner, has adopted new sanitary controls -- requiring workers to wash their hands and installing foot baths to keep their boots clean (WSJ 21Feb08).

Where a Drug Begins

- The plant can produce 800 kilograms to 1,000 kilograms a year, compared to about six kilograms a month at the old-style Yuan Intestine & Casing Factory (WSJ 21Feb08).

Where a Drug Begins

- Pulp is collected and fed through stainless steel pipes into large, covered metal tanks, where it is heated and mixed with a series of chemicals to extract the heparin (WSJ 21Feb08).

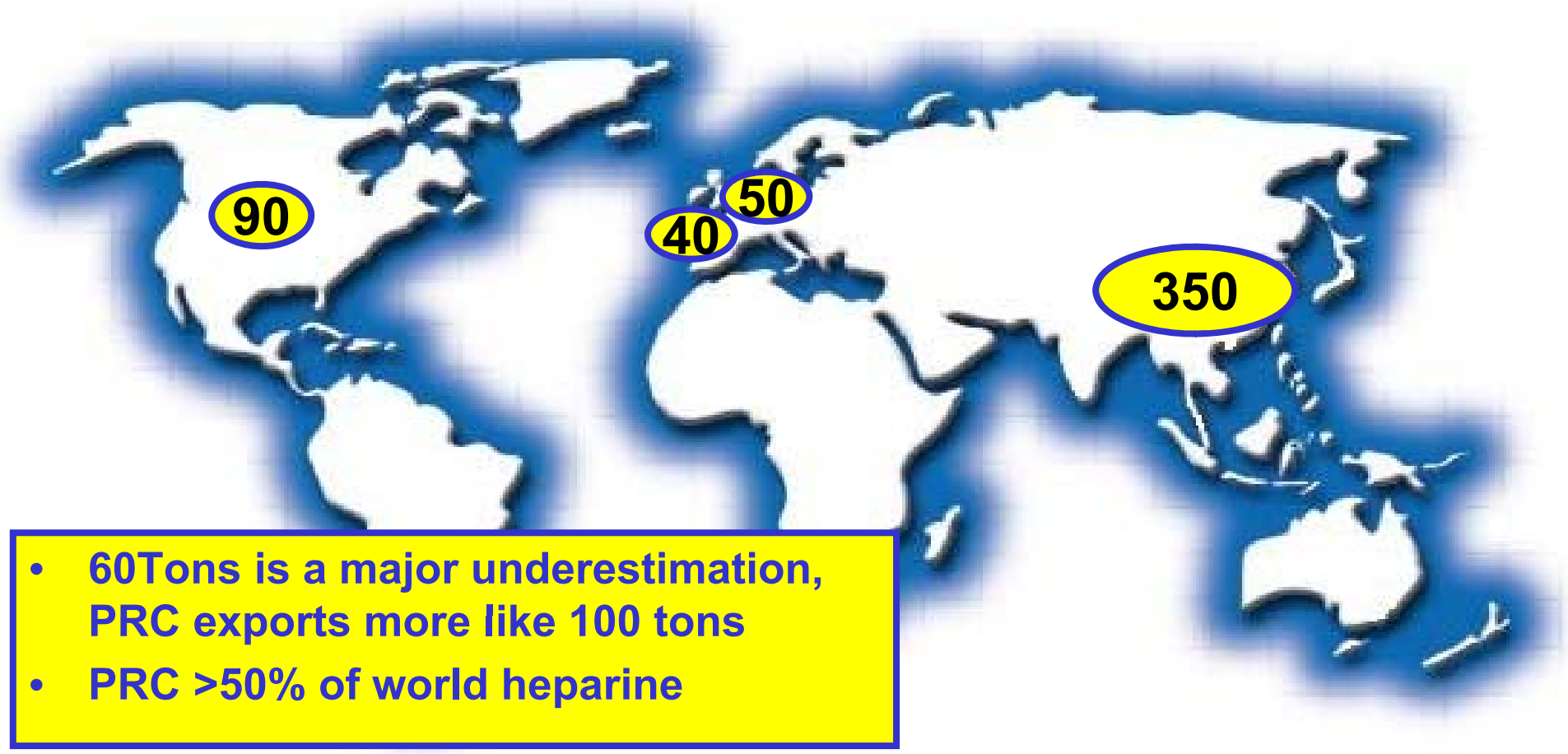
Where a Drug Begins

- Mr. Wang says that his company keeps careful records on which slaughterhouse's pigs are used to produce different batches of heparin. But he says tracing pigs back to individual farms is impractical, since slaughterhouse records aren't detailed enough (WSJ 21Feb08)

As a reference point

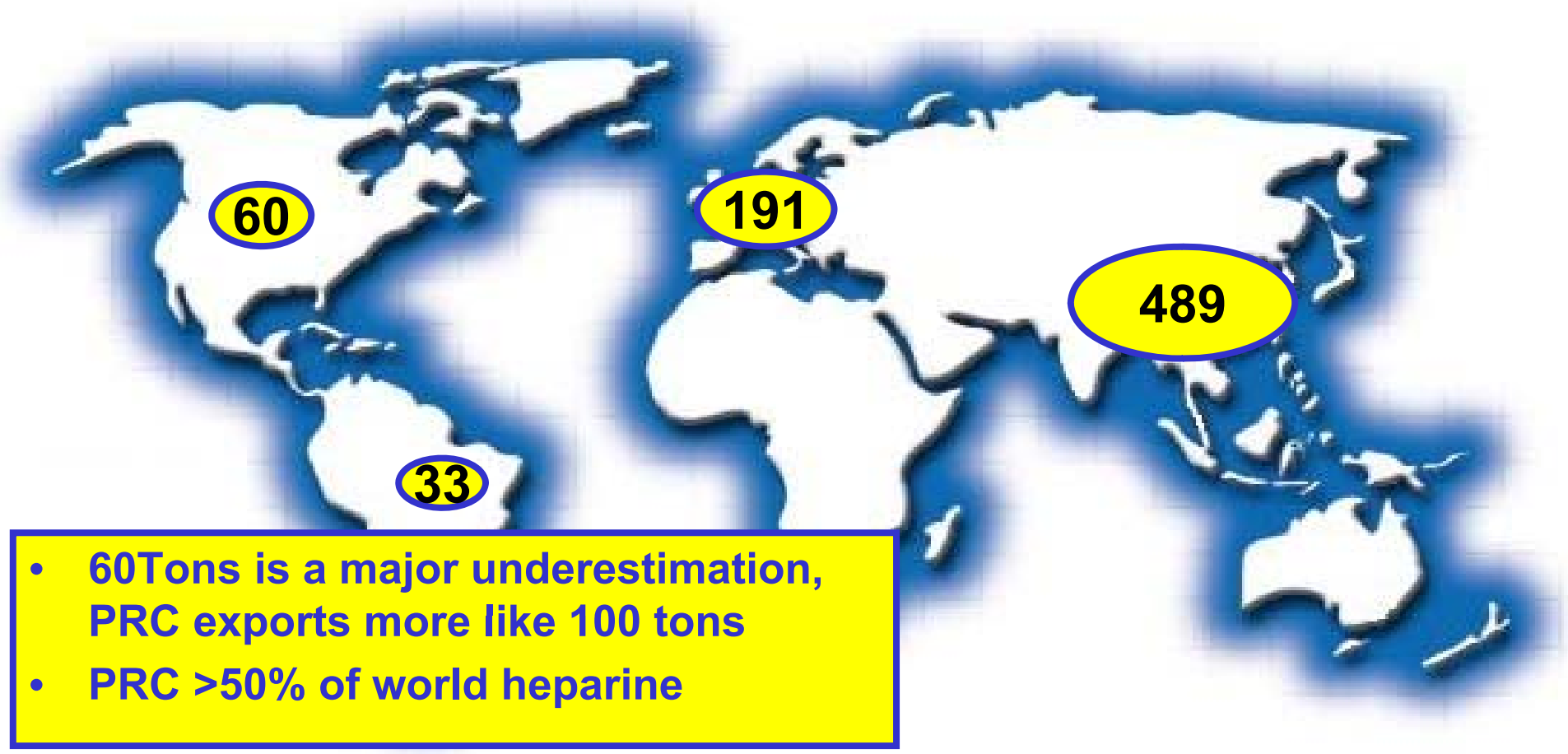
- Now follow a set of photos of a Western location - workshops are located inside or very close to the slaughter houses where intestines are immediately wringed and mucosa (pulp) carried by refrigerated trucks to large manufacturing units.
- Note that traceabilityof each pig from date of birth to slaughter day is achieved in both EU and USA.

Number of slaughtered pigs annually - in million, industry expert



- 60Tons is a major underestimation, PRC exports more like 100 tons
- PRC >50% of world heparine

Number of pigs - in million
FAO statistics



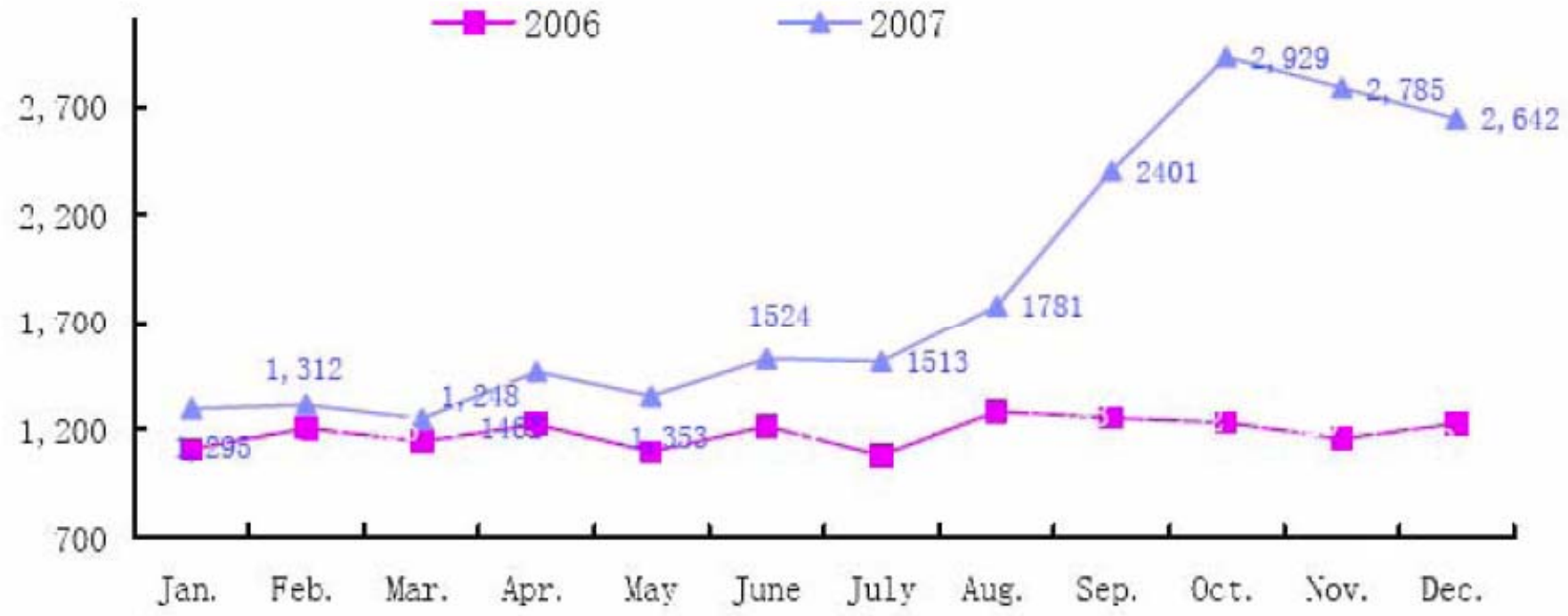
- 60Tons is a major underestimation, PRC exports more like 100 tons
- PRC >50% of world heparine

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

Export of Pure Heparin			
Monthly export of pure heparin in 2007			
Month	Quantity (kg)	Value ($)	Price ($/kg)
Jan.	4,662	6,038,155	1,295
Feb.	6,531	8,569,284	1,312
Mar.	6,055	7,555,608	1,248
Apr.	3,936	5,755,394	1,462
May	9,578	12,962,534	1,353
June	4,821	7,346,315	1,524
July	2,820	4,265,347	1,513
Aug	5,890	10,488,700	1,781
Sep	4,117	9,885,454	2,401
Oct.	2,146	6,284,933	2,929
Nov.	2,835	7,894,283	2,785
Dec.	6,777	17,904,350	2,642
Total	60,168	104,950,357	1,744

Unit: $/Kg

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

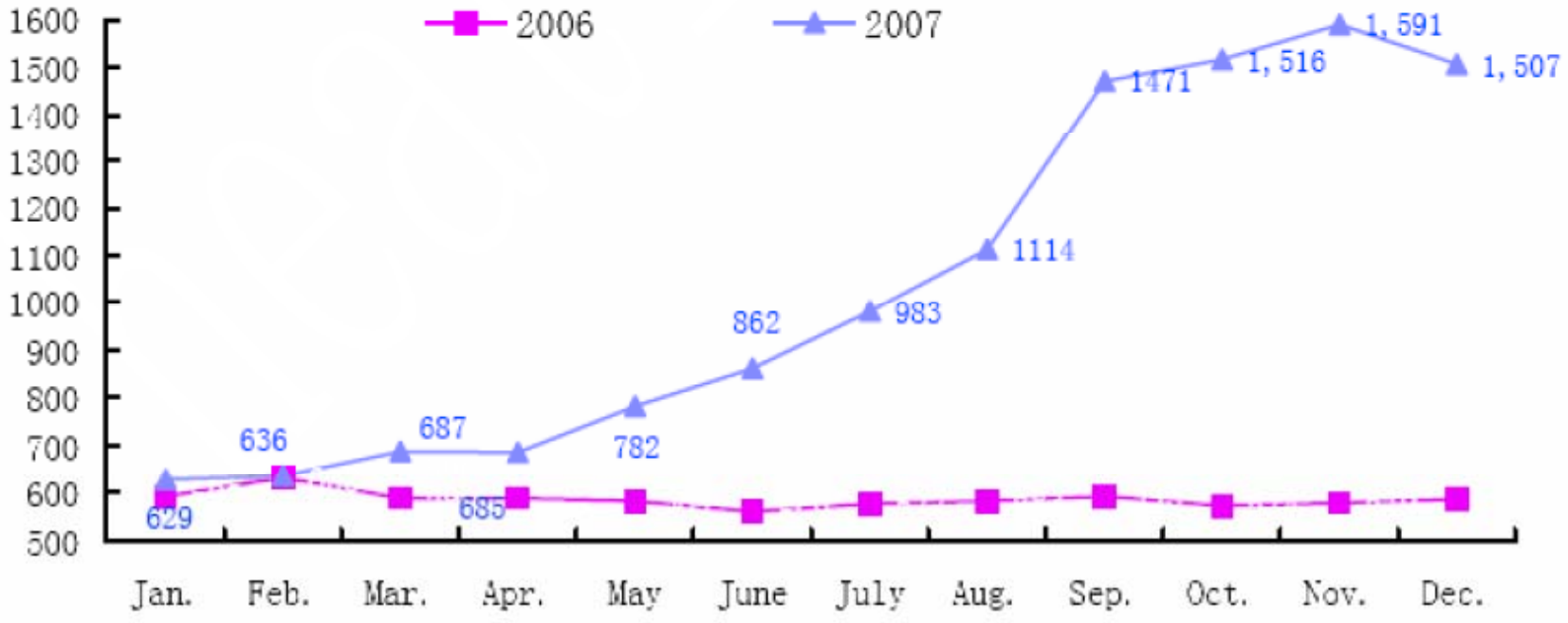


August 2007:
A Flag for all to see:
PRC Export & Price of Crude Heparin

Export of Crude Heparin			
Monthly export of crude heparin in 2007			
Month	Quantity (kg)	Value ($)	Price ($/kg)
Jan.	1,051	661,495	629
Feb.	1,146	728,936	636
Mar.	1,391	955,015	687
Apr.	2,410	1,650,879	685
May	1,074	840,061	782
June	2,491	2,146,271	862
July	2,039	2,004,849	983
Aug	2,077	2,313,527	1,114
Sep	1,081	1,590,295	1,471
Oct.	2,980	4,518,486	1,516
Nov.	2,362	3,758,093	1,591
Dec.	3,450	5,200,118	1,507
Total	23,552	26,368,025	1,120

Unit: $/Kg

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



The previous slides prompted the following comments from the market:

Comment 1:

- In 2006 the level of price in MU was inferior than the graph indicates,
- During 2007 the price of pure (EP grade) went from
  - USD 7 / MU in January 2007, to
  - USD 15 / MU in September 2007

Comment 2

May 2008:

- Crude USD 20 / MU
- Pure USD 25 /UM
- Upward trend

1997/1998:

- Pure USD 4.5 / UM

Widely fluctuating cycles, with fight for margin in the supply chain: purifiers .vs. brokers

Table 13 Exporters Stats on 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	Yanzhou Haolian Casing Co., Ltd	148	207,220	0.25%	1,400
14	QingdaoKangyuanPharmaceuticalCo., Ltd.	140	322,612	0.23%	2,304
15	Zaozhuang Futai Biological Products Co., Ltd	138	228,614	0.23%	1,657
16	Zaozbuang Sainuokang Biochemical Co., Ltd.	100	95,000	0.17%	950
17	Zhenjiang Huacheng Electronics Imp. & Exp. Corp.	92	267,264	0.15%	2,905
18	Nanjing Qian Se Company Ltd.	91	169,296	0.15%	1,860
19	SinochemJiangsuCorporation	72	113,529	0.12%	1,577
20	Yantai Hepu Biological Products Co., Ltd.	50	109,200	0.08%	2,184
21	SHANGHAI SYN	37	40,300	0.06%	1,089
22	Liaoning Pharm	22	39,166	0.04%	1,780
23	Jiangsu Guotai	12	15,240	0.02%	1,270
24	Shenzhen Tech	11	25,033	0.02%	2,276
25	NanchangLifeng	5	7,200	0.01%	1,440
26	China Jiangsu I	3	4,260	0.00%	1,420
27	Argosi Internatio	2	4,890	0.00%	2,445
28	Liaoning Chemi	1	1,545	0.00%	1,545
29	Sichuan Sun-Ri	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

Table 15 Exporters Share of Pure Heparin in Global Regions

Region	Ezporters	Quantity (%g)	Value ($)	Qua'tity Percentage	Price ($/kg)
Europe	Shenzhen Hepalink Pharmaceutical	12, 062	20.05%	15, 889, 750	1, 317
	Changzhou Qianhong Bio-Pharma	9,942	16.52%	18,032,298	1,814
	Yinan Dongyuan Bioengineering Co.,	5, 928	9.85%	10, 626, 768	1, 793
	Shen Zhen Spread Import & Export	5, 375	8.93%	12, 109, 989	2, 253
	Chongqing Imperial Bio-Chem.Co.,	2, 332	3.88%	3, 399, 983	1, 458
	Nanjing King-Friend Biochemical	2, 218	3.69%	3, 202, 780	1, 444
	Shanghai No. 1 Biochemical &	1, 247	2.07%	2, 252, 617	1, 806
	Hebei Changshan Biochemical	973	1.62%	1,669,127	1, 715
	Dongying Tiandong Biochemical	351	0.58%	355, 904	1, 014
	Shanghai Biofine Intemational Co.,	160	0.27%	247, 783	1, 549
	China Jiangsu Medicines And Health	155	0.26%	157, 207	1, 014
	Yanzhou Haolian Casing Co., Ltd	148	0.25%	207, 220	1,400
	QingdaoKangyuan Pharmaceutical	140	0.23%	322, 612	2, 304
	Zaozhuang Futai Biological Products	138	0.23%	228, 614	1, 657
	SHANGHAI SYNNAD CHEMFCAL	37	0.06%	40, 300	1, 089
	Liaoning Pharmaceutical Foreign	22	0.04%	39, 166	1, 780
	Nanchang Lifeng Industry And	5	0.01%	7, 200	1, 440
	Subtotal	**41, 233**	**68.53%**	**68, 789, 318**	**1, 668**

PRC Exporters of Pure Heparin to Europe only - 2007 exporters

- **17 producers; Producers >< exporters >< CEP holders**
- **Wide price fluctuation, and**
  - **Average price to Europe $1668/kg**
  - **Average price to North America $1942/kg**

Table 12 Exporter Percentages 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	6,660,851	5.59%	1,983
7	Danmark	1,125	1,404,194	1.87%	1,248
8	White Russia	980	1,453,864	1.63%	1,484
9	India	931	1,598,367	1.55%	1,718
10	Netherlands	710	1,429,465	1.18%	2,013
11	Uruguay	566	769,877	0.94%	1,360
12	New Zealand	183	247,707	0.30%	1,354
					2,523
					860
					1,092
					1,514
					1,554
					2,701
					1,860
					1,370
					1,577
					1,625
					1,724
					3,108
					623
					1,606
27	Japan				
28	Roumania				
29	South Afri				
30	Mexico				
31	Lithuania				
32	Ukrainc				
33	Switzerlan				
34	Nicaragua				
35	Argentina				
36	Hongkong				
37	Czech				
38	North Kore				
39	Colombia				
	Total				

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.

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.**

API Market Value – USA only
Data from IMS

	Sales value USD million	Kilos sold (in weight Low molecular weight - not KG ex.China)	$ rank	Value rank
2000	108	902	261	444
2002	97	1076	345	468
2006	135	1262	365	454

Notes:

- The view from marketeer of Heparin
  - Kilos grow
  - Price fluctuates

NB:

Pure Heparin from China costs $2500/kg

Heparin formulations retail at: $100.000 for one kg

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 Oganici	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						

middlemen
Producers / Purifiers
likely purifiers
No view

Attempting to explain flows

~APP ?

~Pfizer Fragmine ?

~Aventis Lovenox ?

Top	Exporter	Kg	%	n 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%				0.6			1.2
7	Changzhou Kaipu Biochemistry Co.Ltd.	3,518	6%							
8	Shanghai No. 1 Biochemical & Pharmaceutical Co.	3,390	6%							
9	Shanghai Biofine International Co., Ltd.	1,107	2%	0.9			0.4			
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)

Costs along the supply chain

- 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 respiratpry 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.

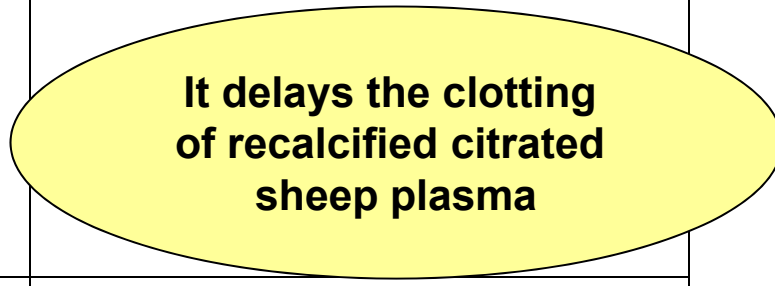
The key issue

- The issue in CHINA has always been the traceability from the pigs to the export companies. For example the major Chinese producers are now doing P.C.R test on the starting material - mucosa - for detecting the presence of other animal species like bovine or sheep and have improved the documentation of batch records.

Bad Science

- A polysaccharide over-sulfation is described in WO/2005/058976 by treating in DMF with pyridine-SO3 complex, (18h 45ºC) 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 sulfate chondroitin producers…

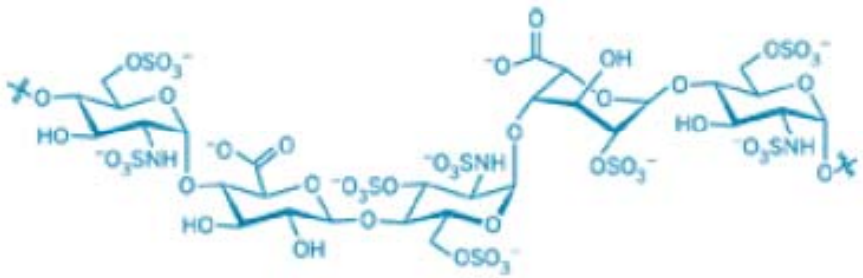
Test name	EP Limit	USP Limit
Description	A white or almost white powder, ►hygroscopic◄, freely soluble in water.	----------
Identification	A. It delays the clotting of recalcified citrated sheep plasma B. specific optical rotation NLT + 35 C. The ratio of the mobility of the principal band or bands in the electropherogram obtained with the test solution to the mobility of the band in the electropherogram obtained with the reference solution is 0.9 to 1.1. D. The residue obtained in the test for sulphated ash (see Tests) gives reaction (a) of sodium	It meets the requirements of the flame test for Sodium
Appearance of solution	The solution is clear and not more intensely coloured than intensity 5 of the range of reference solutions of the most appropriate colour	----------
pH	The pH of the solution is 5.5 to 8.0.	between 5.0 and 7.5, in a solution (1 in 100).
otein and nucleotidic impurities	The absorbance measured at 260 nm is not greater than 0.20 and that measured at 280 nm is not greater than 0.15.	To 1 mL of a solution (1 in 100) add 5 drops of trichloroacetic acid solution (1 in 5): no precipitate or turbidity forms
Nitrogen	Not more than 2.5 per cent, calculated with reference to the dried substance	between 1.3% and 2.5%, calculated on the dried basis, the procedure for Nitrates and Nitrates Absent being used
Sodium	9.5 per cent to 12.5 per cent of Na, calculated with reference to the dried substance and determined by atomic absorption spectrometry	----------
Heavy metals	0.5 g complies with limit test C for heavy metals (30 ppm)	Method II: 0.003%.
Loss on drying	Not more than 8.0%	not more than 5.0%
Sulphated ash (EP) **Residue on Ignition (USP)**	30% to 43%	between 28.0% and 41.0%
Bacterial endotoxins	less than 0.01 IU per IU of heparin, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for removal of bacterial endotoxins.	It contains not more than 0.03 USP Endotoxin Unit per USP Heparin Unit (The USP Heparin Unit is defined by the USP Heparin Sodium Reference Standard and can be independent of International Units)
ASSAY	The estimated potency is NLT 90% and NMT 111% of the stated potency. The confidence limits of the estimated potency (P = 0.95) are NLT 80% NMT 125% of the stated potency	NLT 140 USP Heparin Units in each mg and NLT90.0% and NMT 110.0%of the potency stated on the label.
Anti-Factor X_a activity	----------	Not less than 80% and not more than 120%
Residual Solvents	----------	Meets the requirements
Particulate matter	----------	----------
Other requirements	----------	----------

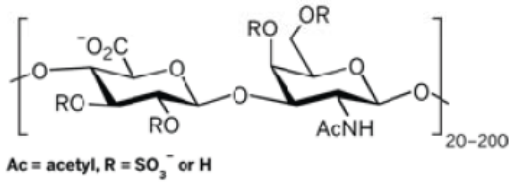


FDA identifies contaminant as oversulfated chondroitin sulfate

C&EN 24Mar08

FDA announced on March 19 that in collaboration with academic labs it has identified a contaminant in heparin linked to severe allergic reactions to the drug. The contaminant is chondroitin sulfate (CS), which like heparin is a variably sulfated glycosaminoglycan. CS is found in cartilage and commonly used in the U.S. as a dietary supplement to treat arthritis.





Complex The antithrombin-III binding domain of heparin illustrates the chemical variety of the drug.

CONTAMINANT The natural product chondroitin sulfate, already variably sulfated, was chemically modified to introduce additional sulfate groups.

In particular, the CS found in heparin was chemically modified with additional sulfate groups. Such oversulfated, or hypersulfated, CS is not known to exist biologically, and thus it would not have been incorporated into heparin products as an artifact of purification, said Janet Woodcock, director of FDA's Center for Drug Evaluation & Research. Unlike typical CS, oversulfated CS mimics heparin in standard regulatory tests, including potency assays. There is little clinical information on the biological properties of oversulfated heparin, Woodcock added.

Crime scenario ?

- What data do we have ?
- What can we assume ?
- Would the crime be profitable ?
- How was it done ?
  - Chondroitin sulfate origin: animal cartilage
  - Chondroitin sulfate is cheap ($20-80)
  - Contaminant is not a natural compound => synthesized!
  - Most likely added deliberately
  - Molecular structure closely resembles heparin
  - Proof obtained that it caused the toxic effects
  - China denies contaminant is cause of deaths and accuses Baxter

How much profit ?

- Hard data
  - 100 tons are exported
  - Shortage/Price hike over last quarter
  - Contamination from less than 1% to 50%;
  - FDA found contaminant in product from 12 PRC heparin producers, as from 2006
- Counterfeit Hypothesis - estimated data
  - During 4 to 12 months 33% of exports with average 10% contamination by weight
  - Low end: 100 / 3 / 3 x 10% = 1 ton
  - High end: 100 / 1 / 3 x 10% = 3 tons

of specially prepared non-detectable contaminant was deliberately, surreptitiously and criminally added to the supply chain

Cost of Oversulfated Chondroitin Sulfate

- Price of Chondroitin Sulfate basic quality (not oversulfated) was approx USD 80 / kg.
- For chondroitin sulfate FOB Beijing (recent quote)
  - 100 kg USD 54 / kg
  - 500 kg USD 53.5 / kg
  - 1000 kg USD 53 / kg

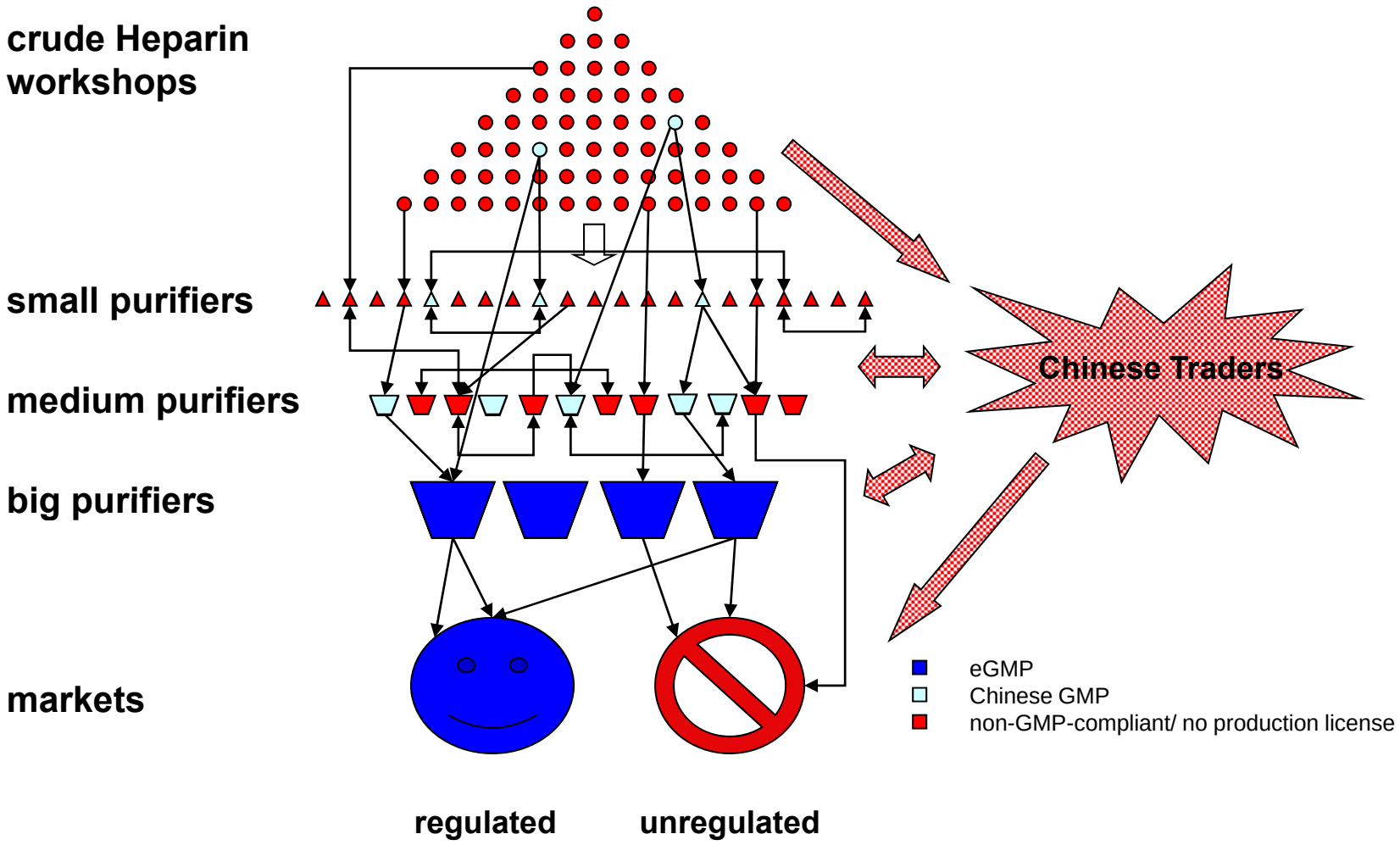
- Synthetic transformation is simple, needs no purification depending whether mixed with crude heparin for purification
  - Estimated production cost for 0.5 ton scale
    - If in a European plant under GMP: $100 / kg
    - If in China: $30 / kg

Profit of Chondroitin fraud

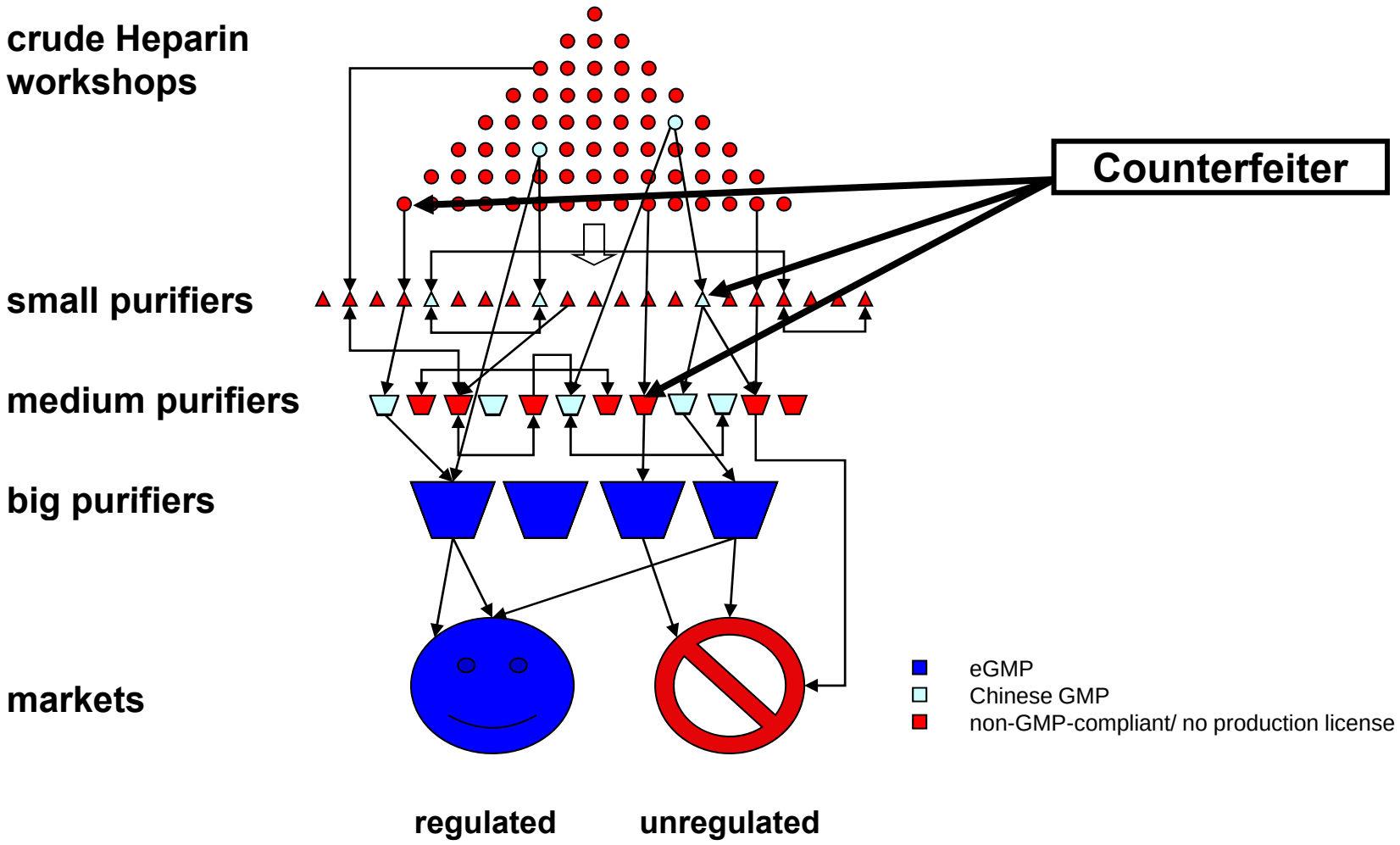
- Raw material cost + transformation + transport + profit = <$100/kg total cost
- To replace Heparin that has a cost upwards of $1000/kg
- Net Profit margin >90%
- Net Profit per ton >$1m
- Total profit $1m to >$3m

- Where to introduce it into the supply chain ?
  - For lowest likelyhood of being found out…
    - early in the supply chain
    - into non-GMP activities
  - But further down-stream would be more profitable

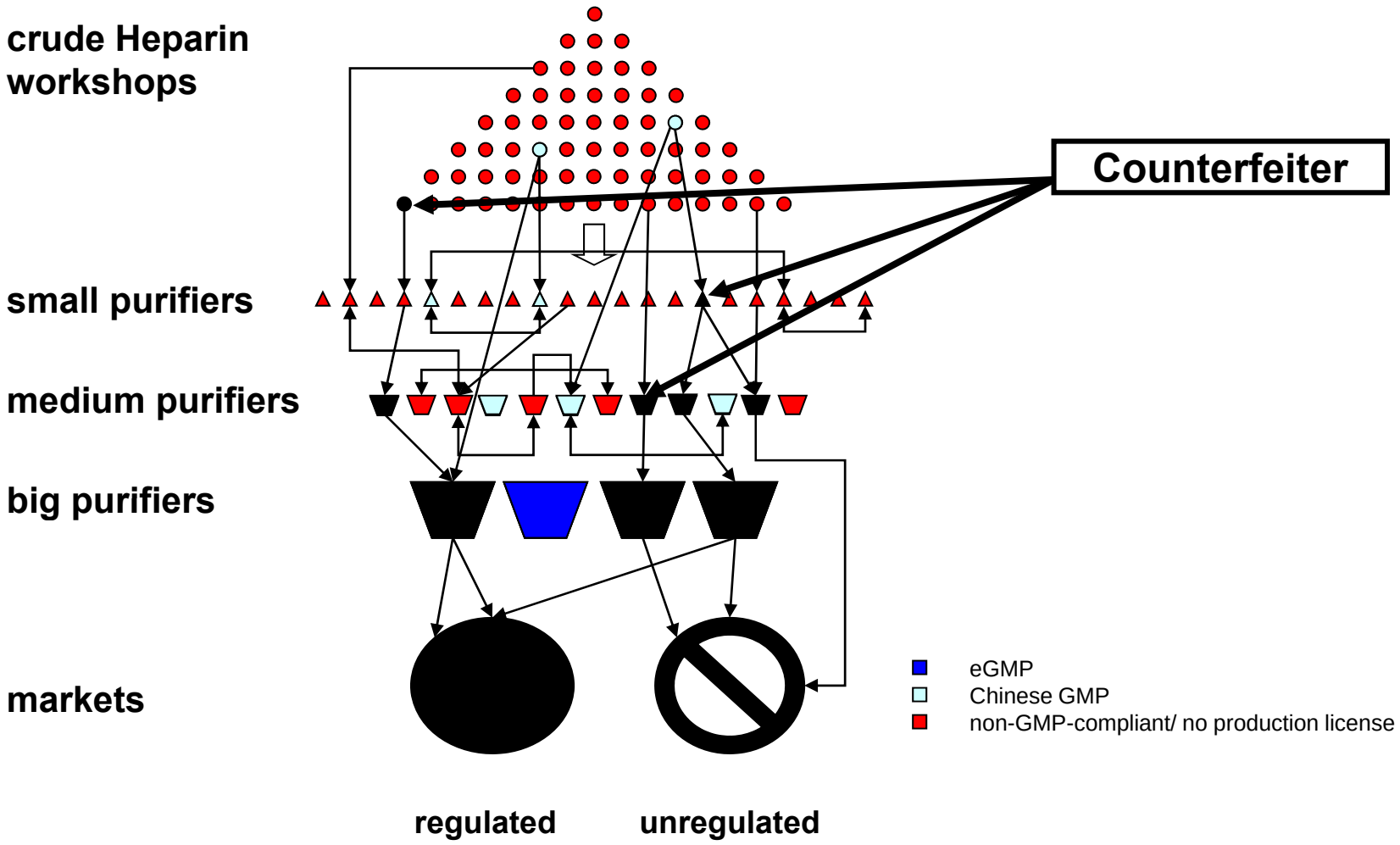
Chinese Heparin Supply Chain (reality)



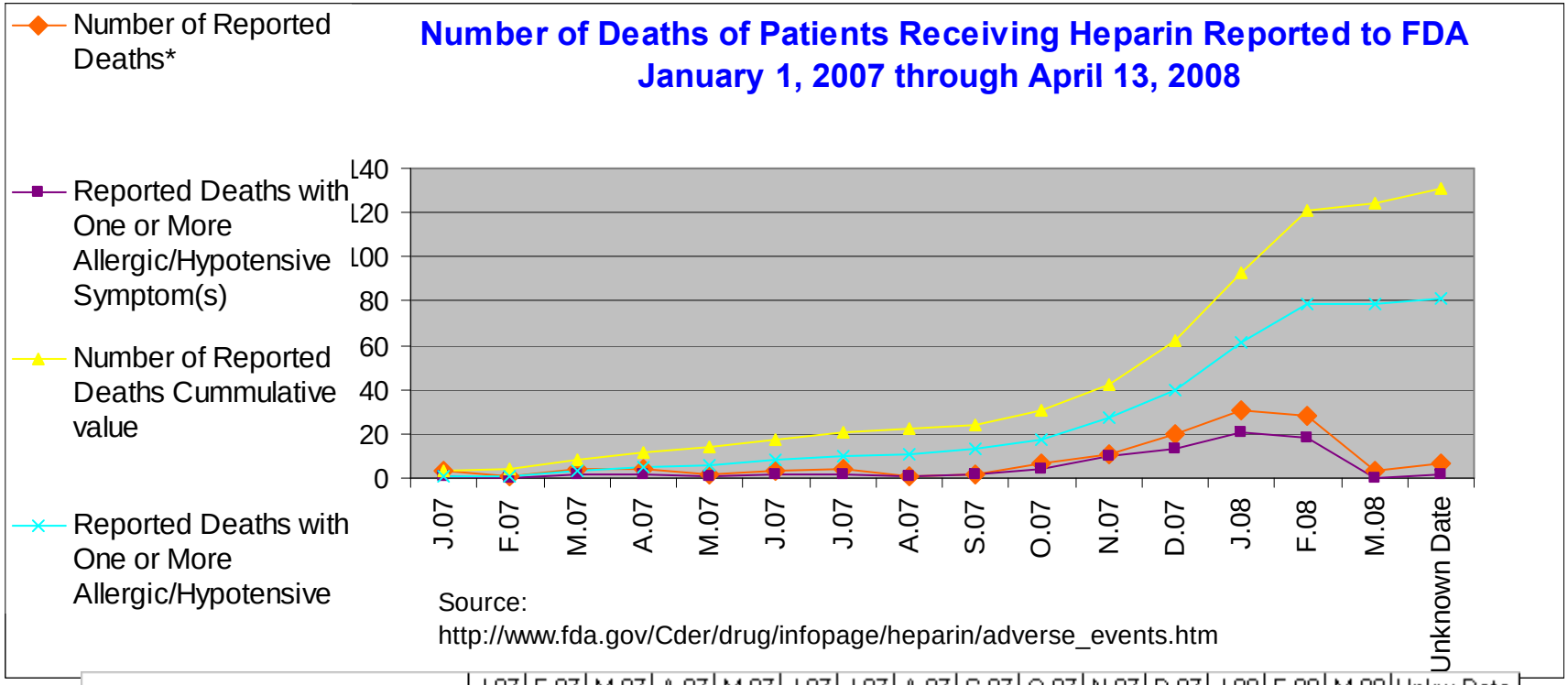
Chinese Heparin Supply Chain (crime hypothesis)



Chinese Heparin Supply Chain (crime hypothesis)



Deaths



Source:
http://www.fda.gov/Cder/drug/infopage/heparin/adverse_events.htm

	J.07	F.07	M.07	A.07	M.07	J.07	J.07	A.07	S.07	O.07	N.07	D.07	J.08	F.08	M.08	Unkw Date
Number of Reported Deaths*	**3**	**1**	**4**	**4**	**2**	**3**	**4**	**1**	**2**	**7**	**11**	**20**	**31**	**28**	**3**	**7**
Reported Deaths with One or More Allergic/Hypotensive Symptom(s)	1	0	2	2	1	2	2	1	2	4	10	13	21	18	0	2
Number of Reported Deaths Cummulative value	3	4	8	12	14	17	21	22	24	31	42	62	93	121	124	131
Reported Deaths with One or More Allergic/Hypotensive Symptom(s) Cummulative value	**1**	**1**	**3**	**5**	**6**	**8**	**10**	**11**	**13**	**17**	**27**	**40**	**61**	**79**	**79**	**81**

Deaths

Heparin 2008: re-cap

	2007						2008												
	Oct	Oct	Nov	Nov	Dec	Dec	Jan	Jan	Feb	Feb	Mar	Mar	Apr	Apr	May	May	Jun	Jun	
Heparin export price	Price More than Doubles																		
Issue become front page news									11Feb										
2007 cummulative USA deaths Nº	17		27		40		61		79										
No EU deaths														AFSSAPS accepts that contaminated product will remain on the market - views as better than shortage					
Recalls USA								Baxter recalls 28Jan				Bbraun							
Recalls ROW										Germany France Denmark Italy Japan			Suisse Sweeden Australia						
Batches contaminated											20 out of 28 at	6 out of 8							
Content of contaminant											5 to 20% in USA			0,1 to 7% in France					
Nature of contaminant established											FDA 6Mar								
														11 countries					

Press mentioned: Baxter, B Braun, Rotexmedica (Panpharma), Opocrin, Aventis, Astra Zeneca, Terumo, Otsuka, Fuso, Gross Apotheke..,

Contaminated heparin found in:

Australia, Canada, China, Denmark, France, Germany, Italy, Japan, Netherlands, New Zealand, Portugal, USA - as at 22April08.

USA vs. Europe

USA

- **Transparent Communications**
  - **FDA announces Baxter recall on 11Feb08 “involves "bolus" doses -- high doses given by health care providers over a short time. The cases don't involve lower doses or slower infusions”**
  - **German authorities write to Doctors on 5th March, FDA publicly discloses the German recall on 6th March**
  - **Still Zero Deaths in Europe – despite twice the population and a 3x higher import volume of Chinese Heparin than the US**
  - **No adulterated heparin is allowed on the market**

Europe

- **Other than the Figaro, why so little coverage by European papers ?**
- **German side-effects and recalls are made public by FDA’s Janet Woodcock in Washington press conference on March 6th**
- **Known to be adulterated Heparin drug product is allowed to remain on the market by several EU medicines’ agencies (France, Belgium.... shortage...), are Medicine Agencies abdicating their responsibility ?**
- **No deaths in Europe !?**
  - **EU: lower concentrations,**
  - **Sub-cutaneous applications appear not to trigger (acute) adverse effects, preferred in Europe, In US intravenous is more widely used**

Conclusions

- This is not simply a regulatory failure, this is not just an issue of Quality Systems, or of lack of inspections
- There is a strong case to believe a crime was committed
- EP is revising their Heparin monograph – why ?

  Revising Monographs is not a preventive anti-counterfeit measure, but only a reactive response to an event in the past. Much more is needed!

  – Criminals aim to be one step ahead
  – What will be the next contaminant ?

Conclusions

- **Penny wise, pound foolish**

  Pure Heparin from China costs $2500/kg

  Heparin formulations retail at: $100.000 for one kg

- **Where were the QPs, the QA ?**
- **Where was the CEO that said Finance could not over-rule QA ?**

- **81 deaths, brands damaged, likely damages in the $bns**

Next Steps

- US FDA Commissioner Von Eschenbach has asked Congress for $275m to protect the US Citizens by bringing oversight over foreign establishments in line with domestic
- FDA and EMEA o inspect jointly
- Penalties for non-compliance stiffen in France
- Big Pharma takes stock
- Pfizer scraps its Steroid go-East plan
- FDA Globalization Bill progressing fast
- EU preparing new legislation to combat pharmaceutical counterfeiting, including API counterfeiting

FDA Next Steps

- 500 PAIs in 2009 (in comparison: 332 in the fiscal year 2007)
- "Beyond our Borders Initiative"
  - FDA presence abroad: 13 in China and train Chinese inspectors.
  - increasingly analyse inspection reports from foreign authorities: FDA already signed 30 non-disclosure agreements
  - not supposed to replace own inspections, but rather to help gain important information and set priorities
- Improved IT Structure, expanded Lab Capacities and build up staff
- Track-and-Trace Systems

Dr Woodcock's May 1st before Subcommittee on Health Committee on Energy and Commerce, United States House Representatives on "Discussion Draft Of The 'Food And Drug Administration Globalization Act' Legislation: Drug Safety" complete presentation is available on the Internet at:

http://www.fda.gov/ola/2008/fdaglobalact050108.html

FDA and EMEA to jointly inspect in the USA, EU and abroad

- 26-May-2008 - Guidelines for collaboration between the US Food and Drug Administration (FDA), the European Commission and the European Medicines Agency (EMEA) were agreed at the Transatlantic Economic Council (TEC) 's second meeting.

  One specific aspect of this broad policy is the launching of a pilot scheme for joint FDA and EMEA inspections of pharmaceutical manufacturing facilities in the US and EU.

  In addition it is proposed that the two regulatory bodies undertake joint inspections of active pharmaceutical ingredient (API) facilities in countries outside of the EU and US.

  Doubling up on inspections should ensure high standards and present a united front but may not be practical for all facilities given the increasing regulatory burden.

  Consequently another pilot scheme will try to cultivate an increasingly fluid flow of information between the FDA and EMEA. This entails the sharing of inspection schedules, results and information on inspected manufacturing sites between the two regulatory bodies.

AFSSAPS Next Steps

10th April 2008: CIRCULAIRES CHIMIE SANTE SICOS:

Project on penalties for GMP non-compliance - France.

1. If a GMP certificate is suspended and still used, the penalty is 3 year imprisonment and a 45,000 Euro fine.

2. If we manufacture, import or distribute APIs in France without having done the declaration and descriptive file, the penalty is 30,000 Euro. (We'll have 9 months to get this done from the date of publication of all details).

3. If we don't declare changes to the above mentioned files, the fine is 15,000 €. As an example, a change in QA manager will have to be declared.

Industry has one month to respond to this project.

Pharma company ~comment:

<<I hope other EU countries will take similar measures.

My intended comments:

1. There should also be sanctions for not informing customers of a suspended GMP certificate.

2. Extend the same type of sanctions for use of suspended CEP's or not informing customers of a suspended CEP>>

Big Pharma Next Steps

<<FYI, a good - though unfortunate - learning lesson... greed is the plague of this world, greetings!

1. If the business interest, culture and scope of a supplier are not compatible to our interest, we are not a good match and we develop better options
2. Have an alternative, avoid single sourcing [if feasible]
3. Reliable information, selection, testing, auditing, reviewing in BOTH technical and commercial issues
4. Be on the ground
5. FDA is not infallible>>

April 2008

Big Pharma Next Steps

April 08 – PCS

- September 2005: New effort to outsource later-stage chemical processing of selected PCS products to a Shanghai group.
- PCS decided recently to terminate the Supply Agreement with Shanghai Pharma because did not meet Pfizer EHS standards.
- PCS productions will continue at Kalamazoo unchanged.
- PCS committed to [low-cost outsourcing] strategy and are working on alternatives.
- PCS plan delayed with 2-3 years.

Thank you.

For more information, please contact:

Guy Villax

gvillax@hovione.com

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E T Isim, C Mauger, C Oldenhof, H Leblanc

Fatal Ingredients

A worrying pattern emerges:

Product	Origin	Deliberate	Where Deaths	Comments
Heparin/OCS (Counterfeit)	China	Yes	US, not in EU	- Side effects in Germany - Mimics in analyses
Pet Food/Melamine (Counterfeit)	China	Yes	US, not in EU	- Mimics in analyses
Gentamicin sulfate (Counterfeit)	China	Yes	US, not in EU	- Only seen with special analyses - Germany reacts: Würzburg project
Glycerin/DEG (Counterfeit)	China	Yes	Not in US/EU	- But found in US/EU: In toothpaste
L-Tryptophan (Not a counterfeit)	Japan	No	US, not in EU	- Trace impurity - Side effects in Germany