Aktuelle analytische Erkenntnisse zu weltweiten Arzneimittelfälschungen

Ulrike Holzgrabe

Chair of the working group
„Arzneimittelsicherheit/Arzneimittelfälschung“
of the German Pharmaceutical Society (DPhG)
University of Würzburg

Die Erde hat genug
für jedermanns Bedürfnisse,
aber nicht für jedermanns Gier

Mahatma Gandhi

Schaden durch Produktpiraterie:
30 Mrd. Euro = 7 % Welthandelsvolumens
CDs, DVDs, Armbanduhren, Brillen, Handtaschen,
Sportartikel, etc. und **auch Arzneimittel**

Vom Zoll beschlagnahmte Waren

BR 5, Juni 2012

24 % Medikamente

21 % Verpackungen (z. B. Müsliboxen)

18 % Zigaretten

73 % der beschlagnahmten Waren kamen aus China!

MEDIKAMENTE

Tödliche Imitate

Kriminelle, die Handel mit gefälschten Medikamenten treiben, gefährden Menschenleben und verdienen Milliarden. Wissenschaftler entwickeln jetzt Methoden, um ihnen das Handwerk zu legen.

Bild der Wissenschaft, September 2012

2012

Supporting Organisations:

The 3rd University of Würzburg Anti-Counterfeit Conference

Strategies against Falsified/ Counterfeit Medicines

How to Establish Anti-Counterfeit Strategies in Pharmaceutical Companies

7 - 8 May 2012
Würzburg (near Frankfurt), Germany

SPEAKERS:

Dr Hans-Joachim Bigalke
EDQM, France

Dr Thomas Hecker
EDQM, France

Prof Dr Ulrike Holzgrabe
University of Würzburg, Germany

Andreas Maack
Merck KGaA, Germany

Dieter Mößner
Carl Edelmann GmbH, Germany

Michael Levy
FDA, USA (invited)

Dr Stephan Schwarze
Bayer Pharma AG, Germany

Dr Bernd Renger
European QP Association, Germany

Dr Mona Tawab
ZL, Germany

Dr Hermann Thöne
Novartis Pharma AG, Switzerland

Dr Christian Tillmanns
Meisterernst Rechtsanwälte, Germany

HIGHLIGHTS:

- Regulatory Updates:
  - EU Directive on Falsified Medicines – Update and Consequences
  - The Revised EU Good Distribution Practice Guide – Expectations and Concerns
- Setting up, Implementing and Running a Successful Global Anti-counterfeiting Program
- Authentication of Suspect Samples: Recent Examples of Counterfeit Medicines
- Counterfeit Drugs in Europe: Status Quo and Options to Identify them
- Focusing on Falsification/Manipulation during GMP Inspections
- Case Studies for Coding and Track&Trace:
  - EDQM Anti-Counterfeiting Traceability Service for Medicines (eTact)
  - "securPharm" – German Stakeholder Initiative to Avoid Falsified Medicine Reaching Patients
  - The Mobile Authentication Service (MAS)
- Coding / Track & Trace Requirements Worldwide
- Tamper Verification Features for Medicinal Product Packaging
- FDA's Anti-Counterfeit Strategies – Update and Future Activities

Outline

- Definitions, Statistics, Overview of cases
- Heavy metals and contaminated dietary supplements
- Phthalate contamination
- The tryptophan case
- Heparin: OSCS, dermatan, porcine, etc.
- What can be prevented by using a trace and track technology?

Counterfeit drugs

WHO SFFC: Spurious/falsly-labelled/falsified/counterfeit medicines are medicines that are deliberately and fraudently mislabelled with respect to identity and/or source.

Ciprobay against anthrax shortly after 11th September 2001

Tamiflu® counterfeits in expectation of a influenza pandemia? May 2007

5 Categories of counterfeits:

- Mislabelled counterfeits
- Counterfeits containing less API
- Counterfeits containing the wrong API
- Counterfeits containing no API
- counterfeits containing substandard APIs

DIRECTIVE 2011/62/EU

Article 1 Definitions

Active substance:

Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in its production, becomes an active ingredient of that product intended to exert a pharmacological, immunological or metabolic action with a view to restoring, correcting or modifying physiological functions or to make a medical diagnosis.

Excipient:

Any constituent of a medicinal product other than the active substance and the packaging material.

Brokering of medicinal products:

All activities in relation to the sale or purchase of medicinal products, except for wholesale distribution, that do not include physical handling and that consist of negotiating independently and on behalf of another legal or natural person.

Article 1 Definitions

Falsified medicinal product:

Any medicinal product with a false representation of:

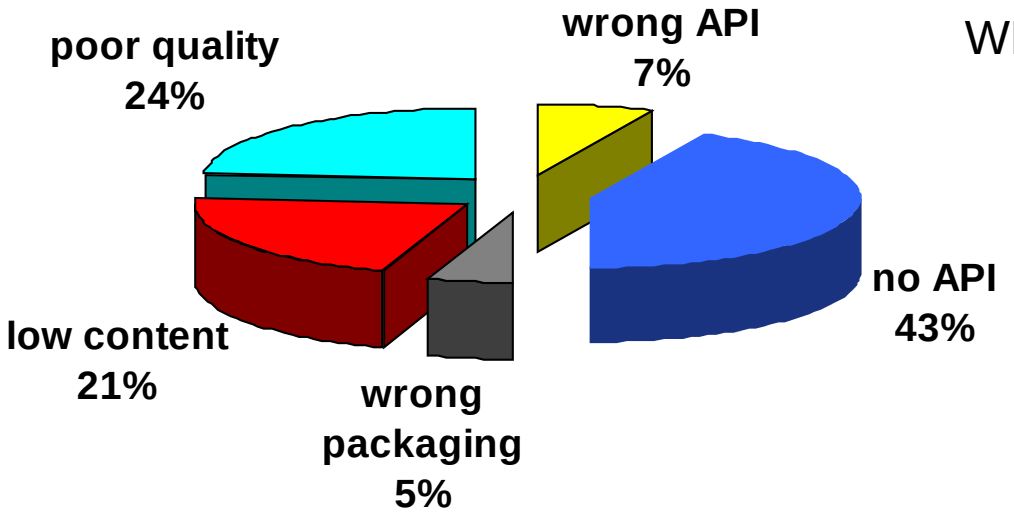
(a) its identity, including its packaging and labelling, its name or its composition as regards any of the ingredients including excipients and the strength of those ingredients;

(b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or

(c) its history, including the records and documents relating to the distribution channels used.

This definition does not include unintentional quality defects and is without prejudice to infringements of intellectual property right.

WHO Counterfeits (2006)



WHO Estimations

Frequency of occurence in different countries

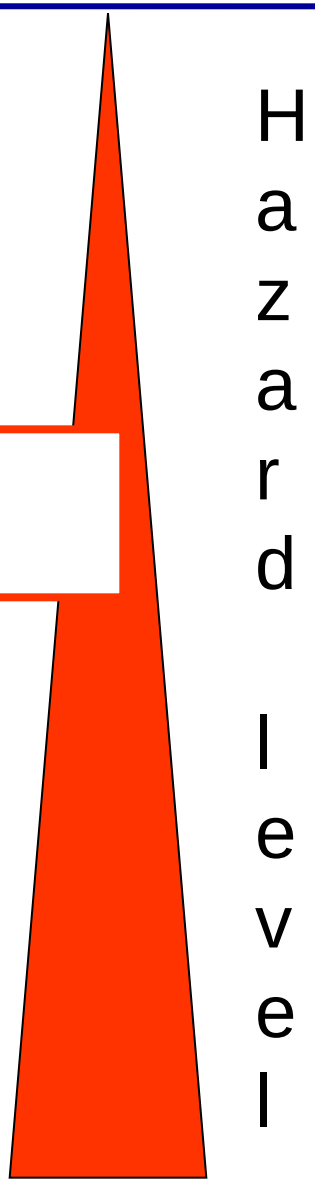
USA	5 - 7 %
GUS	> 20 %
Africa	50 – 60 %
Mexico	30 %
Latin America	
South East Asia	

German Pharma Health Fund eV.

Novartis experiences (2011)

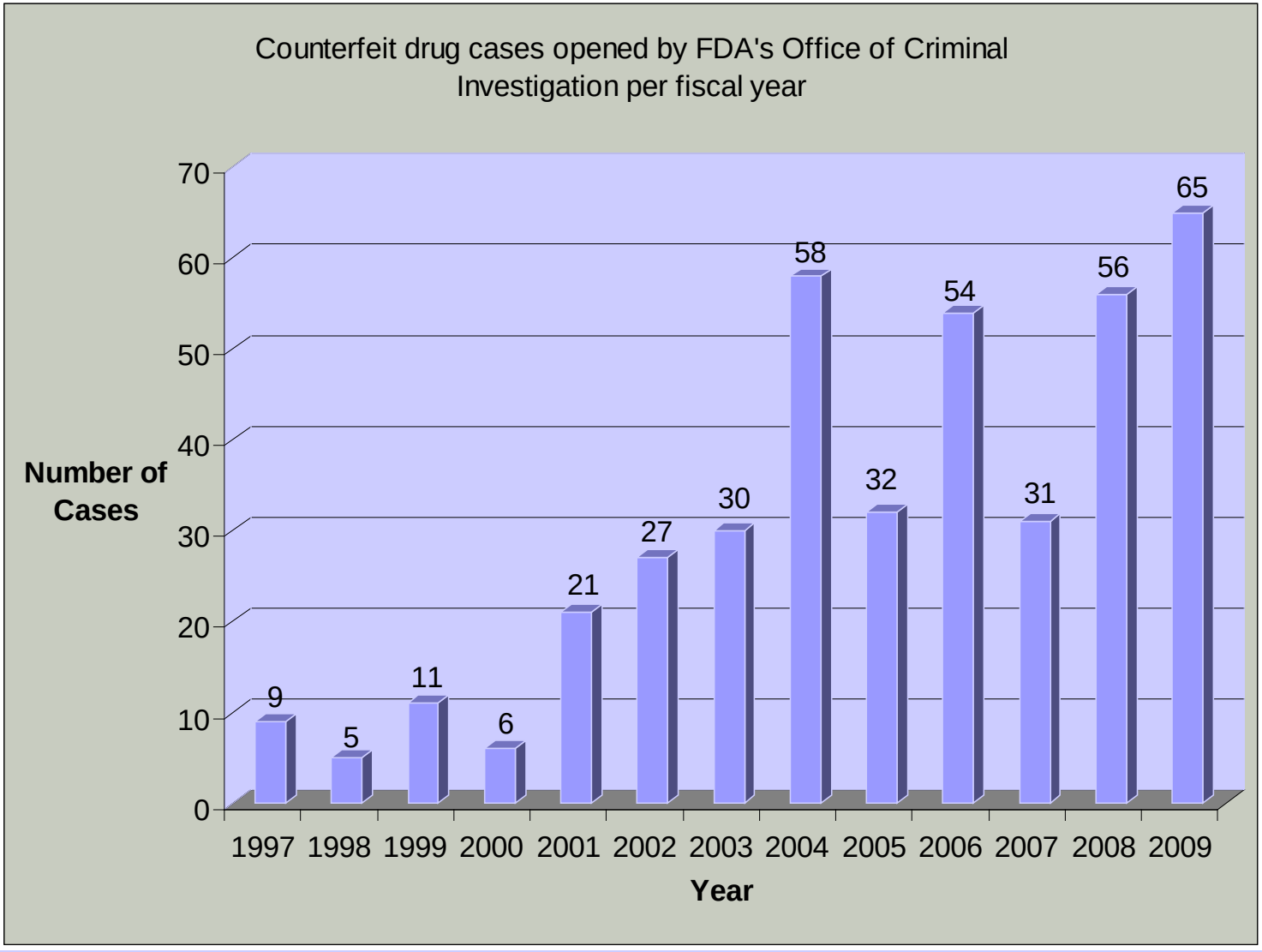
Counterfeit product characteristics	Incidence rate [%]
Counterfeit products in genuine primary & secondary packaging; re-used from waste	Sporadic cases
100 +/- 30 % of declared API (frequently substandard, rarely decent quality	25
Genuine product, but manipulated, e.g. expired and shelf life extended, repacked for illegal parallel trade, fraudulent labeling (100 mg instead of 50 or 25 mg)	15

6 cases at Novartis



H.J. Thöne, Novartis Pharma AG, Basel,
Strategies against falsified/counterfeit Medicines

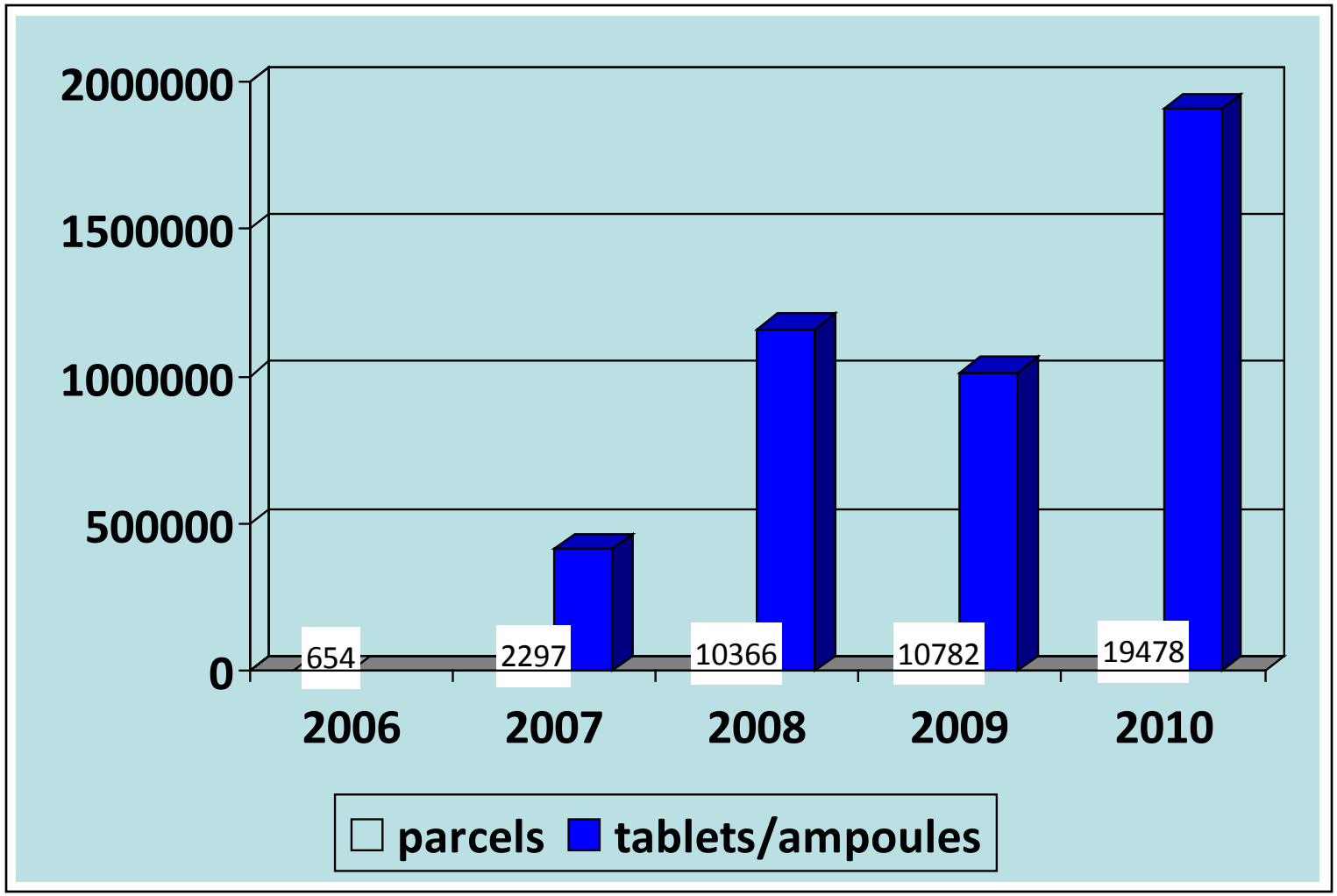
USA and China



In 2001, approximately 200.000 people in China died from counterfeit drugs; 2012 2000 Fälscher gefangen genommen!

Securing illegal drugs at Frankfurt airport

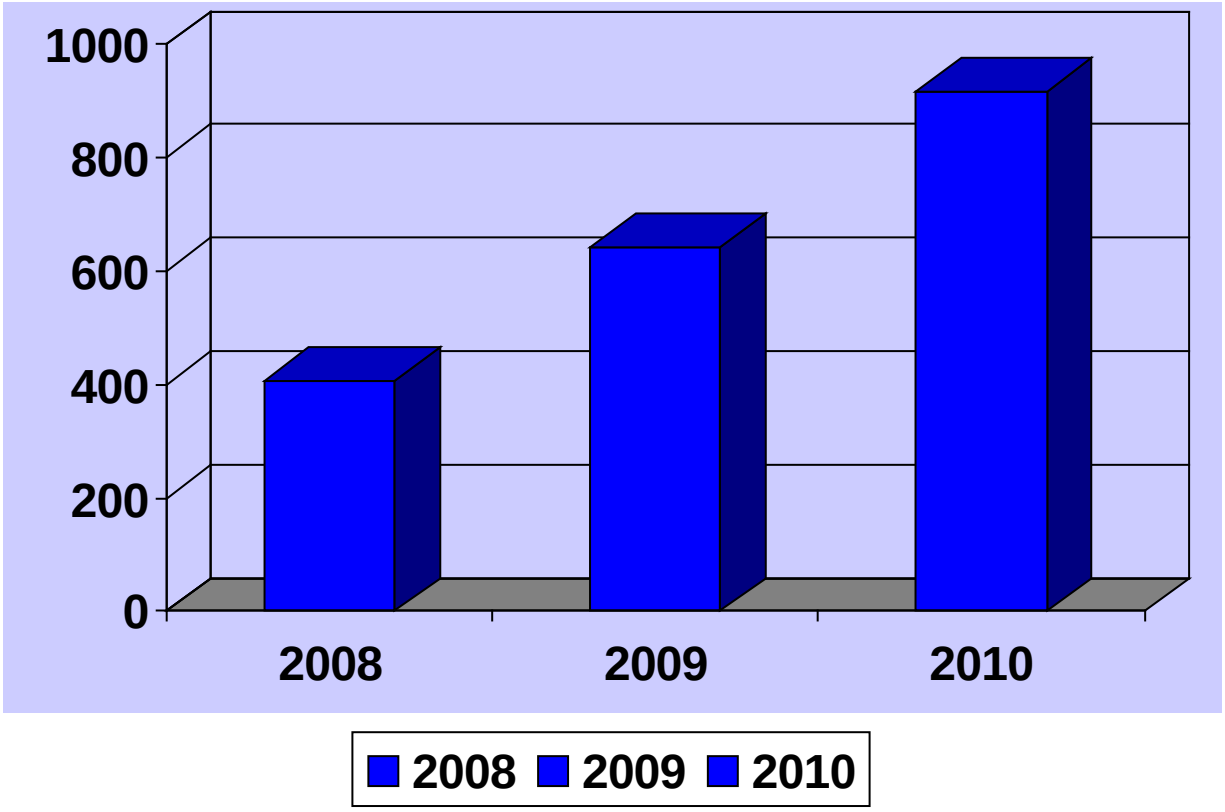
Zollkriminalamt Köln



Estimated annual sales of illegal drugs in Europe
10.5 billion € (Pfizer 2010)

Preliminary proceedings

Zollkriminalamt Köln



Certificate of Suitability to Monographs of EP

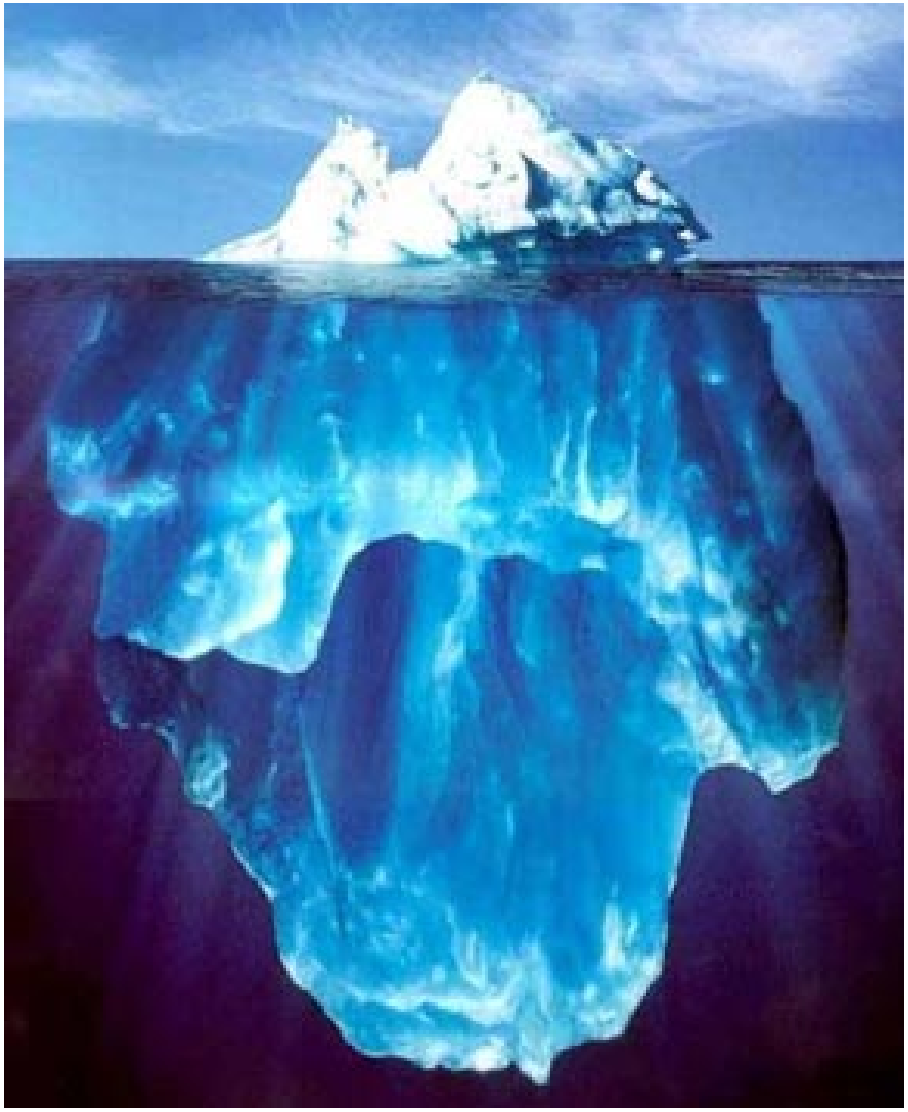
The EDQM has conduced 160 API inspections in China and India in the last 10 years:

More than 50 certificates of suitability (CEP) were suspended or withdrawn

OMCLs, Official Medicinal Control Laboratories

- Independent public laboratories (national laboratories)
- 30 European countries participate in activities of networks
- 80 laboratories or OMCLs pool human and technical resources to implement testing programmes
- About 500 products (by mutual recognition procedure or decentralized procedure) were tested by the network
- 2-3 Market surveillance studies/a
- About 150 counterfeit or illegal products testing were issued in 2010

The tip of the iceberg



Cases recently reported

2012 Adderal (Teva, ADHD, narcolepsy) contained tramadol & acetaminophen instead of dextroamphetamine derivatives

2012 Avastin (bevacizumab) without any API (reported by the FDA February 2012)

2012 Isotab (isosorbide mononitrate) contained pyrimethamine in large quantities (overdose) reported in Pakistan

2011 Plasticizers, e.g. diethylhexyl phthalate, in pharmaceuticals, food and beverages in Hongkong

2010 Clopidogrel was manufactured without consideration of the GMP rules (EMA)

2008 Heparin contaminated with oversulfated chondroitin sulfate (Europe and USA)

2009 Antidiabetic traditional medicine contained 6 x the normal glibenclamid dosis (China)

2007/6 Tamiflu (Oseltamivir) contained metronidazol/ acetaminophen

Cases recently reported

2012 Avastin (bevacizumab) without any API

- Production of Avastin at Genentech, USA
- Hospitals purchased Avastin from a wholesaler from Gainesboro, Tennessee
- The US wholesaler became Avastin from a broker in Canada
- The Canadian broker became Avastin from a British intermediate broker
- The British broker became Avastin from a danish company
- The Danish company became Avastin from a Swiss broker
- The Swiss broker purchased Avastin from an Egyptian tradesman
- The Egyptian tradesman said that he has got Avastin via a Syrian broker from Turkey

I. Glomp, Bild der Wissenschaft, September 2012

Deaths caused by drugs of inaedaquate purity

1990 Paracetamol-syrup contaminated with diethylene glycol originated from glycerol (some 80 deaths)

1990 Tryptophan-Affair: the change in the production process led to additional impurities causing the Eosinophilia-Myalgia-Syndrome (EMS) some 30 deaths

2000 Gentamicin in high concentrations (off-label-use) caused the death of some 60 people in the USA

2007/8 Heparin with anaphylactoid, oversulfated chondroitin sulfate, approx. 100 deaths in USA

2006 onwards Diethylene glycol in glycerin from China:

Diethylene glycol in glycerin

- *1985 Diethylene glycol in Austrian Wine*
- 1990 Paracetamol-syrup contaminated with diethylene glycol originated from glycerol (some 80 deaths)
- 2006 Diethylene glycol in glycerin from China: dozens of deaths in Panama
- 2007 Diethylene glycol in glycerin found in tooth pate in UK
- 2009 Diethylene glycol in glycerin in syrup for teething children in Nigeria

Drugs contaminated with impurities

Cases occurring permanently

- Heavy metals in small organic acids and herbals (TCM, ayurvedic medicines) originated from China
- Dietary supplements of plant origin containing toxic substances such as aristolochia acid (kidney damages) or
- Dietary supplements containing active pharmaceutical ingredients

Outline

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Heavy metals

FDA / Safety / Medwatch, 15th March 2012

Skin creams, Soaps and Lotions Marketed as Skin Lighteners and Anti-aging treatments: May Contain the Toxic Metals, Mercury

FDA notified healthcare professionals and warned consumers not to use skin creams, beauty and antiseptic soaps, or lotions that might contain mercury. The products are marketed as skin lighteners and anti-aging treatments that remove age spots, freckles, blemishes and wrinkles. Adolescents also may use these products as acne treatments. Products with toxic metals have been found in at least seven states.

Heavy metals

Industrial gelatin used to make pills: TV report

Globa
By Ya

Fortunately, none of these capsules reached the European and US market.

The capsules, marketed by factories from provinces including Qinghai and Jilin, were found to have a chrome content of over 90 times higher than the national standard in extreme cases, the Weekly Quality Report, a CCTV program committed to exposing quality scandals of various products, revealed Sunday.

The gelatin was produced from leatherSong Xunjie, the manager of Hebei Xueyang Glair and Gelatin Factory, revealed that this kind of gelatin is made from leather leftovers that are supposed to be used in leatherwear, after they were processed with calcium oxide and industrial acid base. Thus, chrome-VI were found in the gelatin.

Heavy metals in herbal drugs & fatty oils

Heavy metals (Pb, Cd, Hg) are natural constituents of the environment, i.e. water, soil and air. Thus, herbals growing in the nature are accumulating heavy metals. E.g. St. John´s worth and birch leafs are accumulating cadmium, urticaria roots and Iceland moss herb lead.

Chinese TCM and Ayurvedic Medicines (L. Kabelitz, 2009)

Mercury	max. 104.000 ppm	} deliberately added (2008)
Arsenic	max. 8.000 ppm	
Lead	max. 37.000 ppm	

“Cases of heavy metal poisoning from the use of traditional remedies are undoubtedly under-reported. This is a particular problem for lead poisoning because of the nonspecific signs and symptoms of toxicity (e.g., tiredness, lethargy, GI disturbances, anaemia and decreased IQ and behavioural problems in children).” E. Lynch & R. Braithwaite 2005

Heavy metals in herbal drugs & fatty oils

Public Health Risks from Heavy Metals and Metalloids Present in Traditional Chinese Medicines

*K. Cooper et al. **J**. Toxicol. Environm. Health 70, 2007, 1694-99*

Out of 247 traditional Chinese medicines (TCM) investigated, a proportion were contaminated with arsenic (5–15%), lead (5%), and mercury (65%). Some preparations exceeded the tolerable daily intake (TDI) for males and females for arsenic (4 and 5 products, respectively), lead (1 and 2 products), and mercury (5 and 7 products). These excedances were as high as **2760-fold**, which posed a potential danger to public health. As many users are known to self-prescribe, there is a substantial risk of poisoning from the consumption of these contaminated TCM.

Heavy metals in herbal drugs & fatty oils

Analysis of Toxic Heavy Metals in Branded Pakistani Herbal Products

M. Saeed J. Chem. Soc. Pakistan, 32, 2010, 471-475

The present study was designed to estimate the concentration of heavy toxic metals in Pakistani herbal products frequently used for the treatment of various ailments. For this purpose, 25 herbal products of well reputed herbal manufacturers were selected. The results of our investigation revealed that the concentrations of lead, cadmium, nickel and chromium were far beyond the permissible limits proposed by the International Regulatory Authorities for herbal drugs. Therefore, this study conveys a strong message to the ministry of health to establish proper rules and regulations for the validation of herbal products on scientific grounds in order to protect the general public from the harmful effects of these heavy metals in herbal products.

Heavy metals in small organic acids

Metals in APIs and Excipients: Salts of small organic acids (samples from Indian Sources)

M. Türck, 2008 Presentation EDQM

Calcium lactate	Cr ~ 25 ppm;	Mn ~ 5 ppm;	Al ~ 5 ppm;
Fe(II) fumarate	Cr 200 - 1000 ppm	Pb 20 – 30 ppm	
NH_4 ferric citrate	Cr 200 ppm	Mn 2500 ppm	

Problem for parenteral use! Limits: Cr 2.5 ppm, Mn 25 ppm

Consequence: Revision of the general method for the determination of heavy metals in the USP and PhEur (in connection with EMA “Guideline on the specification limits for residues of metals catalysts” EMEA/CHMP/SWP/4446/2000, 2008)

Dietary supplements

FOR IMMEDIATE RELEASE – Fort Lauderdale, FL – **April 19, 2012**
XROCK INDUSTRIES, LLC Issues a Voluntary Nationwide Recall of X-ROCK, a Product Marketed as a Dietary Supplement to Support Male Sexual Performance, Due to Unlisted, Potentially Hazardous Ingredient:

Finished product of X-ROCK for Men was tested and preliminarily found to contain an analogue of an ingredient in an FDA-approved drug. Analytical tests conducted by the Food and Drug Administration (FDA) of X-ROCK for Men concluded that the products contained sildenafil and hydroxythiohomo-sildenafil. Hydroxythiohomosildenafil is an analogue of sildenafil. Sildenafil is the active pharmaceutical ingredient in an FDA-approved drug that is used to treat erectile dysfunction (ED).

Dietary supplements

FOR IMMEDIATE RELEASE – Kennesawe, GA – **August 23, 2012**
Evol Nutrition Associates, Inc./Red Dawn ("Evol Nutrition") announced today that it is conducting a voluntary nationwide recall of all lots of two dietary supplement products distributed by the company under the names Mojo Nights and Mojo Nights for her to the comsumers level.

The FDA confirmed that Mojo nights contained the following undeclared APIs: tadalafil, sildenafil, sulfosildenafil, sulfoaildenafil, & hydroxythiohomosildenafil.

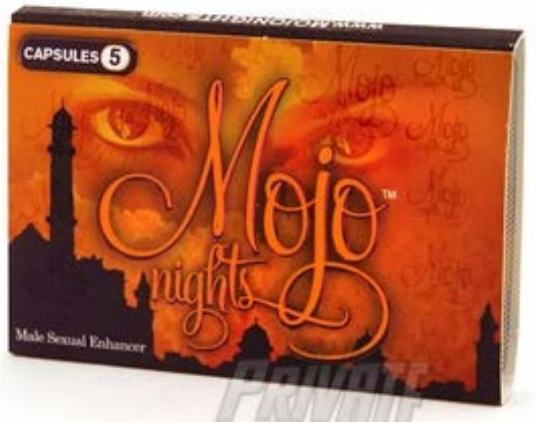
Mojo nights is a male sexual enhancement pill.

ITEM DESCRIPTION

Mojo Nights is a male sexual enhancement pill that claims to jump start your sex drive, give you powerful erections, stop premature ejaculation, and make you feel young again. This 100% natural pill is chock-full of ginseng, ginkgo biloba leaf extract, l-arginine, caffeine and horny goat weed extract. With those ingredients, Mojo Nights might have you bouncing off the walls, using your penis as a pole vault.

Mojo Nights Erection Pills are for men 18 years and older, and last from 3 to 4 days. We haven't tried Mojo Nights yet to see how well it works, but most of the off-brand penis pills have something to them. They seem to help your penis stay hard and give you stamina, rather than fixing erectile dysfunction.

5 Mojo Nights Pills. Made in the USA.



Internet Pharmacies

FDA cracks down on websites selling bad drugs

Reuters – Thu, Oct 4, 2012

Reuters/Reuters - A view shows the U.S. Food and Drug Administration (FDA) headquarters in Silver Spring, Maryland August 14, 2012. REUTERS/Jason Reed

(Reuters) - The U.S. Food and Drug Administration said it has cracked down on thousands of online pharmacies for selling potentially unsafe, unapproved or fake medicines, including the erectile dysfunction drug Viagra and antiviral Tamiflu.
The FDA, working with international regulatory and law enforcement agencies from about 100 countries, said on Thursday that it took action against more than 4,100 Internet pharmacies, bringing civil and criminal charges, removing offending websites and seizing drugs worldwide.

Compounding in a Pharmacy

In a Drug Linked to a Deadly Meningitis Outbreak, a Question of Oversight

By DENISE GRADY, SABRINA TAVERNISE and ANDREW POLLACK
Published: October 4, 2012

The nation's growing outbreak of meningitis, linked to spinal injections for back pain, was a calamity waiting to happen — the result of a lightly regulated type of drug production that had a troubled past colliding with a popular treatment used by millions of Americans a year.

The outbreak, with 5 people dead and 30 ill in six states, is thought to have been caused by a steroid drug contaminated by a fungus. The steroid solution was not made by a major drug company, but was concocted by a pharmacy in Framingham, Mass., called the New England Compounding Center. Compounding pharmacies make their own
not approved by the FDA..

Preservative-free
methylprednisolone acetate (80mg/ml)

Early recognition of substandard quality

Die Notwendigkeit der Untersuchung pharmazeutischer Präparate in chemischen Laboratorien.

Von Dr. Eugen Seel-Stuttgart.

(Eingeg. d. 2./8. 1911.)

(Schluß von S. 2006.)

II. Zusammengesetzte Mittel

einschl. pharmaz. Zubereitungen und Spezialitäten.

1. u. 2. Byrolin und Borglycerinlanolin. Byrolin soll nach der Literatur in der Hauptsache bestehen aus Borsäure, Glycerin und Lanolin, welche Mittel der Namen seines Ersatzpräparates „Borglycerinlanolin“ auch bezeichnet. Nach meinen Untersuchungen[73]) enthält das Byro-

[73]) Pharm. Ztg. 1911, Nr. 35.

Angewandte Chemie 24, 2054-2059 (1911)

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- Definitions, Statistics, Overview of cases
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- **Phthalate contamination**
- The tryptophan case
- Heparin: OSCS, dermatan, porcine, etc.
- What can be prevented by using a trace and track technology?

Phthalate contamination

Phthalate contamination

History

In June 2011, Department of Health in Hong Kong recalled health supplements due to contamination of plasticizer di(ethylhexyl)phthalate (DEHP) in two excipients used as flavouring agents of juice powders and joghurt. Manufacturer of the cloudy agent was located in Taiwan.

The local food additive manufacturer had illegally used DEHP as a substitute for palm oil in emulsifier formulas to cut costs.

Higher dosis than allowed were found in tons of contaminated food, e.g. noodles, cookies, beverages such as pineapple juice, sport drinks, tea drinks, fruit jams, jellies and syrups.

DEHP was found in Augmentin of GSK in Hong Kong, resulting in a recall. However, an overdose could not be confirmed.

Phthalate contamination

DEHP warrant of apprehension

DEHP is produced in 2 million tons/a worldwide and is used primarily as a plasticizer in flexible polyvinyl chloride products. It is not primarily bound to plastic polymers and thus leach from the matrix and become widely distributed in the atmosphere and hydrosphere.

Consumer products: toys, furniture, nail polish, hair spray, as solvent in perfumes and many other cosmetics.

In medical treatments involving infusion, hemodialysis, peritoneal dialysis, parenteral nutritional therapy, patients my be exposed to several milligrams of DHEP from the bags and tubes.

Phthalate contamination

Toxicity

Probable human carcinogenic (classified as class B2 be the US Environmental Protection Agency), developmental and reproductive toxicity, but the reason for toxicity remains to be unclear.

In Cosmetics forbidden in the EU, China, and Taiwan.

In the EU Directive 2005/90/EC, DBP, DEHP, BBP identified as reproductive toxicants.

USA: Draft Guidance for Industry: Limiting the Use of Certain Phthalates as Excipients in CDER-regulated Products (March 2012; 90 days for Comments)

Recommendations: Oral reference doses for DBP 0.1 mg/kg/day; DEHP 0.02 mg/kg/day; search for alternative excipients

Phthalate contamination

Phthalates in the environment

A group of environmental pollutants due to massive use and persistence

Occurrence	**Median**	**Range**	**Detection frequency**
Yangtze River (μg/L)	14.66	0.011-54.73	9/9
Indoor dust (μg/g)	228	9.9-8400	75/75
Soil (μg/g)	121.9	48.0-221.4	10/10
Foodstuff (μg/g)			
Fruit	1.01	0.56-1.68	4/4
Vegetable	2.67	<MDL-4.98	9/11
Dried food	6.00	0.02-30.44	6/6

Wang, Xia, Sha, J. Hazard. Mat. 154 (2008), 317-324

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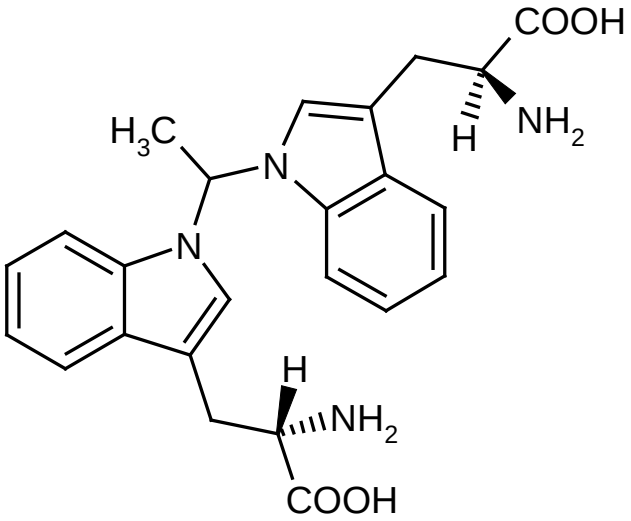
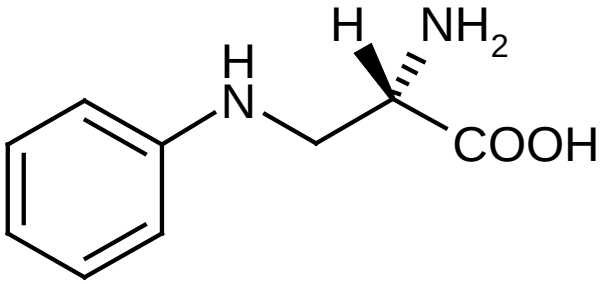
Tryptophan

- Tryptophan is mainly used as food supplement!
- In 1989, many cases of the eosinophilia-myalgia syndrome (EMS) were observed
- In USA: 1500 patients, approx. 30 deaths
- The EMS cases could be traced to the application of tryptophan produced by Showa Denko in Japan
- Changes in the production process
- Search for the unknown impurity

Tryptophan





Peak E: 3,3‘-[Ethylidenbis(1*H*-indol-1,3-diyl)]bis[(2*S*)-2-aminopropionic acid = *1,1-Ethylidenbistryptophan*

Peak UV-5: Amino-3-(phenylamino)-propionic acid = 3-Phenylaminoalanine = PAA

Further impurities: 2-(3-indolylmethyl)-*l*-tryptophan, 2- and 5-hydroxytryptophan, several carboline derivatives and others

Tryptophan

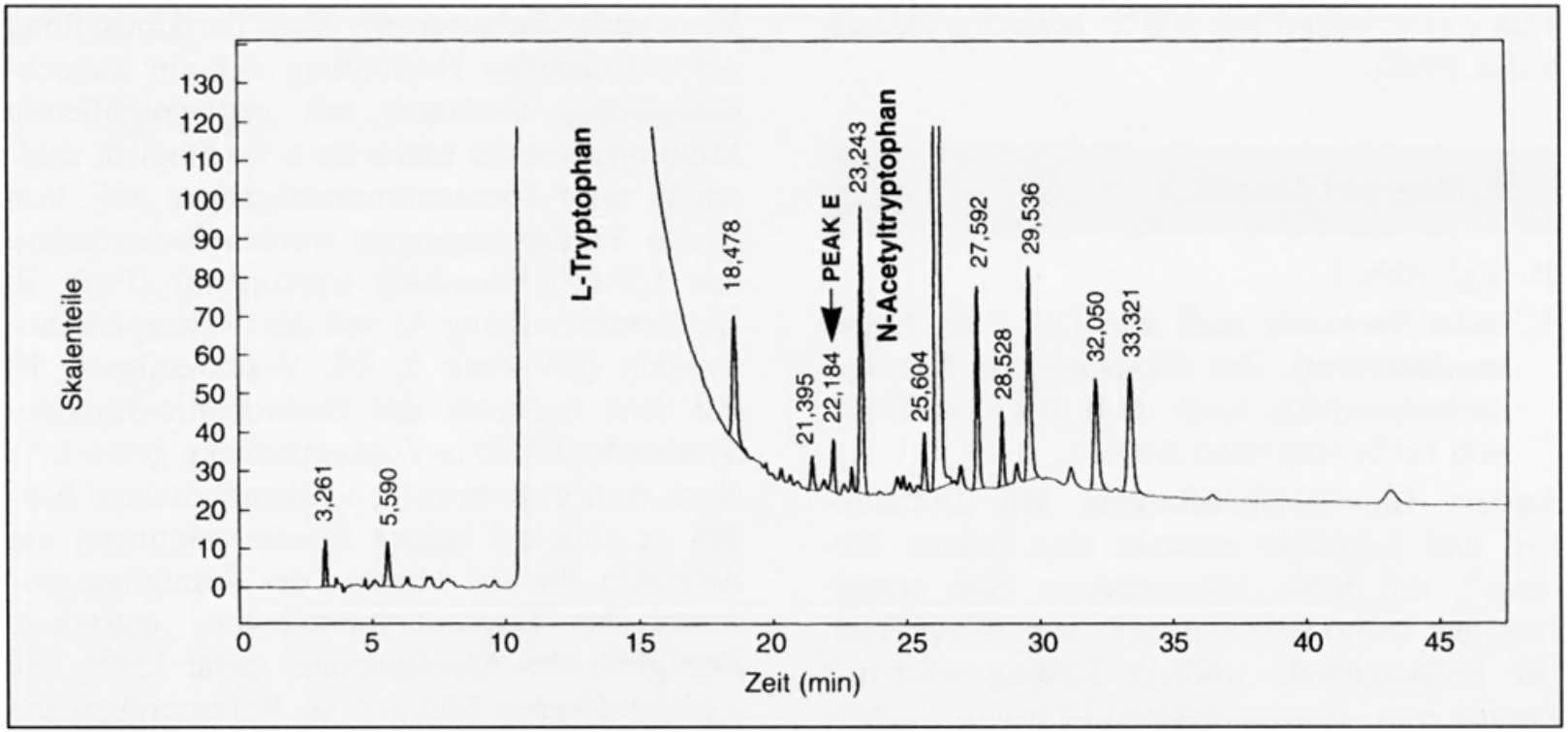


Abb. 3: HPLC-Chromatogramm von verunreinigtem L-Tryptophan (Summe der Verunreinigungen 2921 ppm vor und nach dem Tryptophan-Peak)

Commentary to the European Pharmacopoeia

Tryptophan

Tryptophan-Affair 1989: And today?

Studies from Kyowa Hakko in USA revealed still a low quality in nutritional supplements which are claiming USP standard!

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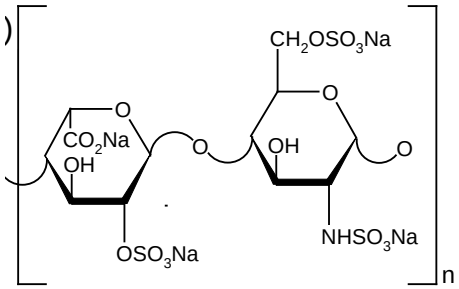
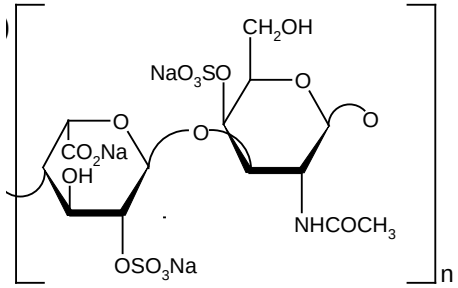
The History

- In 2008, some 900 cases of adverse events associated with the use of heparin were reported to the FDA and the BfArM, some 200 died.
- The adverse events could be assigned to the occurrence of oversulfated chondroitin sulfate in heparin, originated from China (mostly Baxter)
- In the first stage, an NMR and CZE method were developed in order to limit this impurity.
- In the second stage, the NMR method went into the identification section of USP and PhEur, a new anion-exchange HPLC and a new biological assay were introduced in the test section, etc.

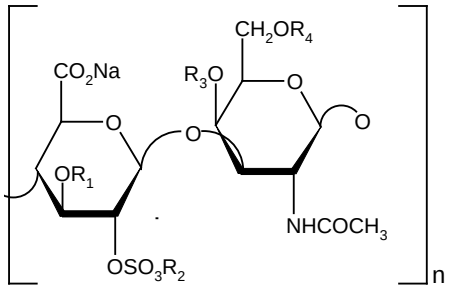
Heparin Case



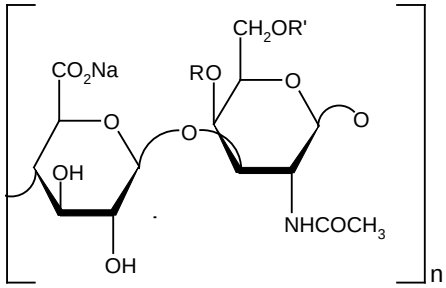
Heparin
Glucosamine + Iduronic acid,
N-acetylated Glucosamine + Glucuronic acid



Dermatan sulfate
Galactosamine + Iduronic acid

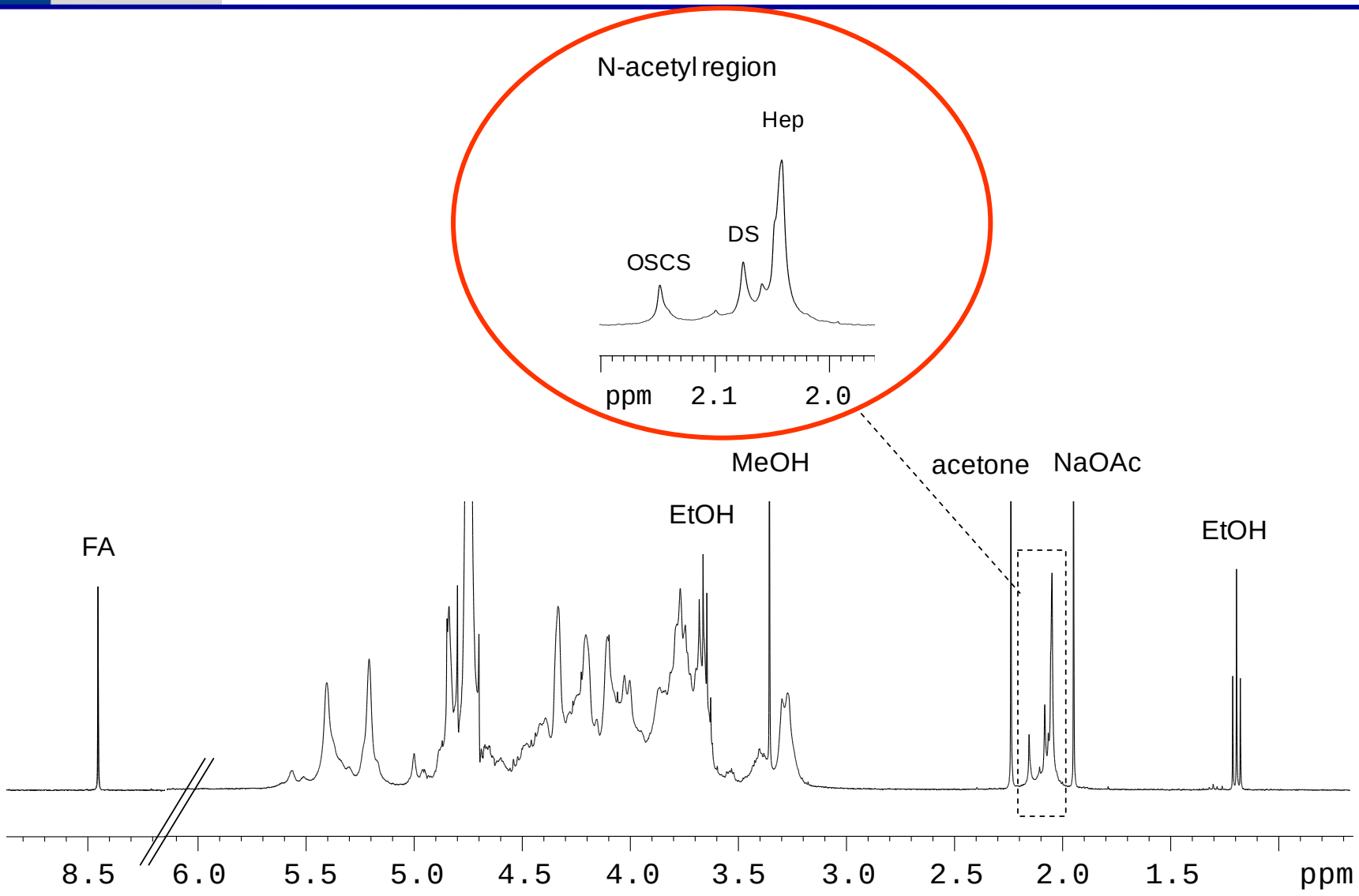


„oversulfated“ Chondroitin sulfate
Galactosamine + Glucuronic acid
R_1-R_4 = sulfated
OSCS



Chondroitin sulfate A/C
Galactosamine + Glucuronic acid
R = R´ = sulfated

Heparin ^{1}H NMR spectrum



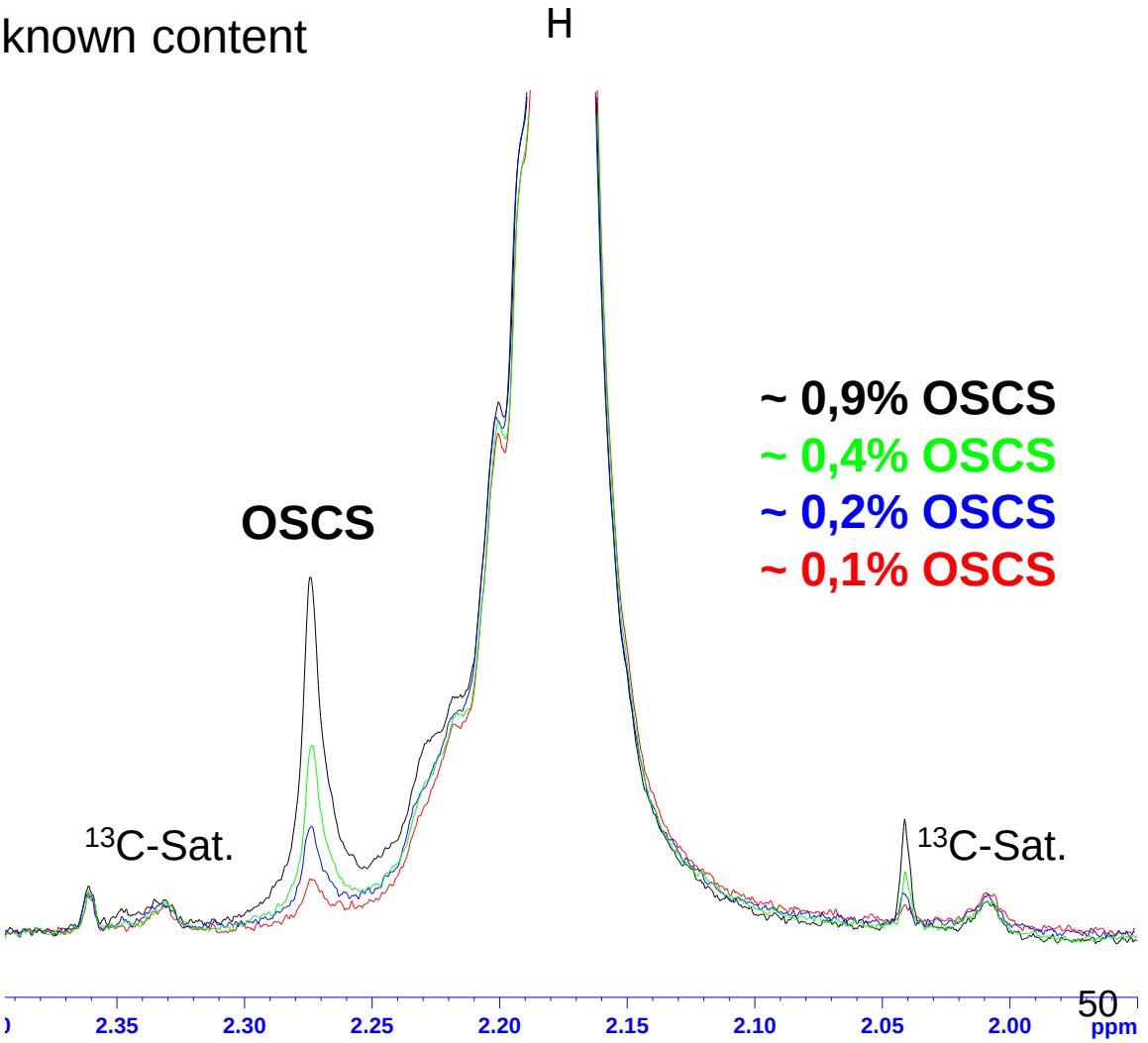
Heparin – LOD NMR

1) pure Heparin spiked with OSCS
2) pure Heparin spiked with
   contaminated Heparin of known content

<u>Experimental parameters</u>

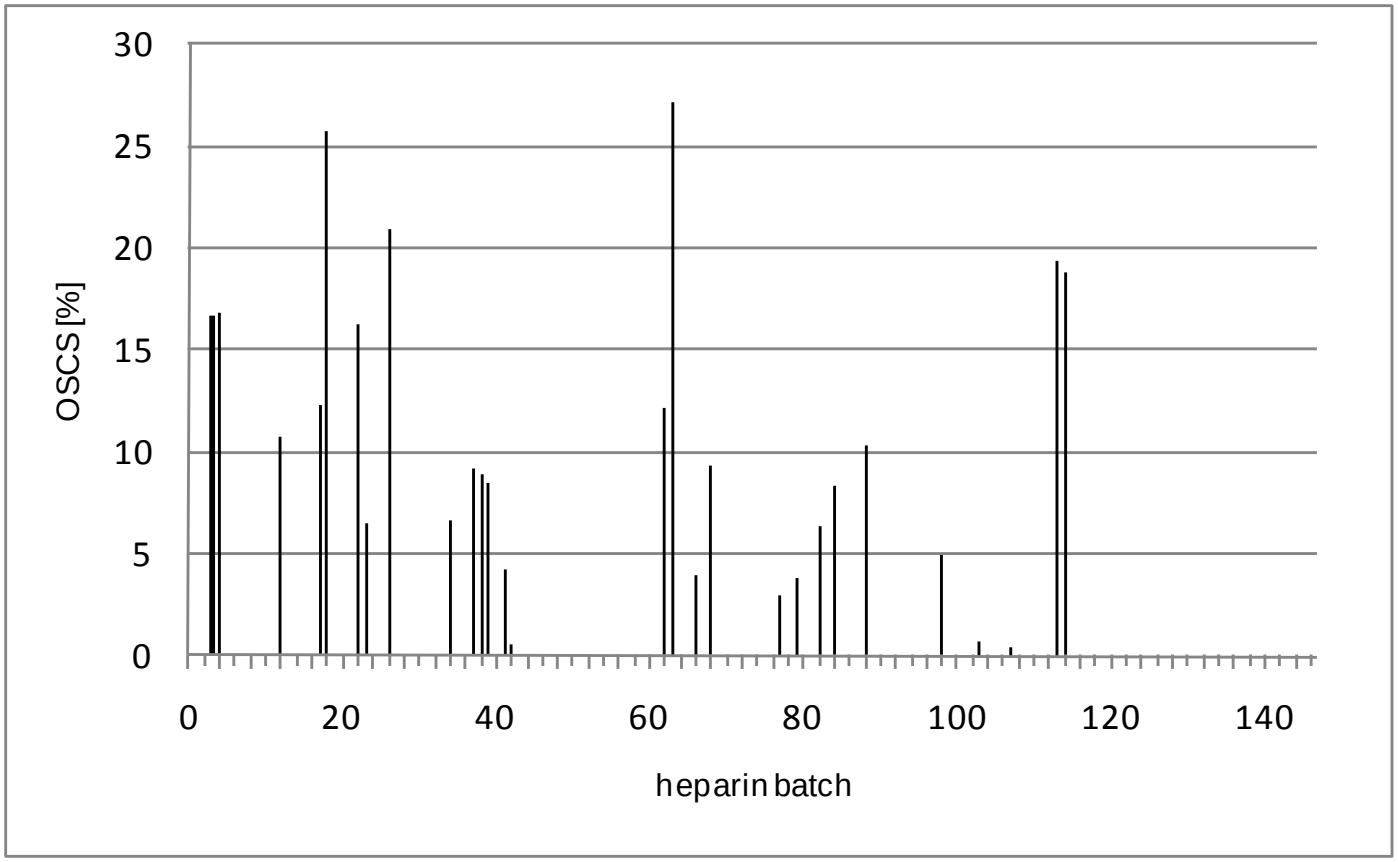
- 400 MHz
- 90˚-Puls (*versus* 30˚)
- NS = 128
- T_1 (CH_3) = 1,44s ’ 5 x T_1
- T = 315K (*versus* 353K)
- Mt = ~ 18min

LOD = 0.1 % !



T. Beyer, B. Diehl, G. Randel, E. Humpfer, H. Schäfer, M. Spraul, C. Schollmayer, U. Holzgrabe, J. Pharm. Biomed. Anal. 48 (2008) 13-9, and Pharmeuropa Bio 2008-1, 31-39

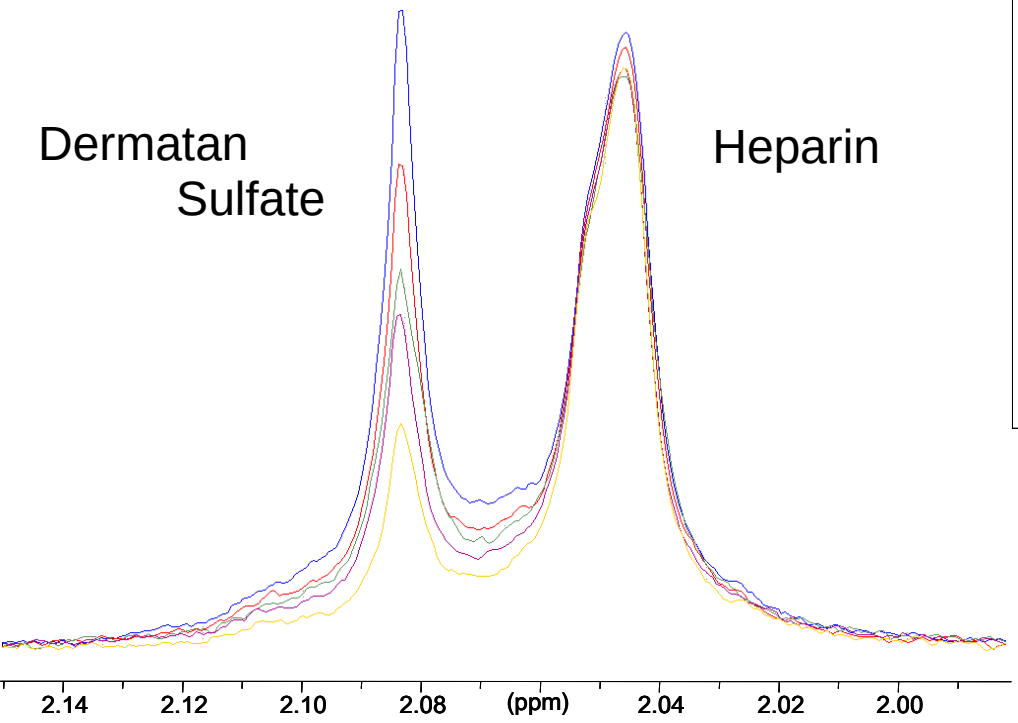
Analysis of ~ 150 batches in Germany content of OSCS

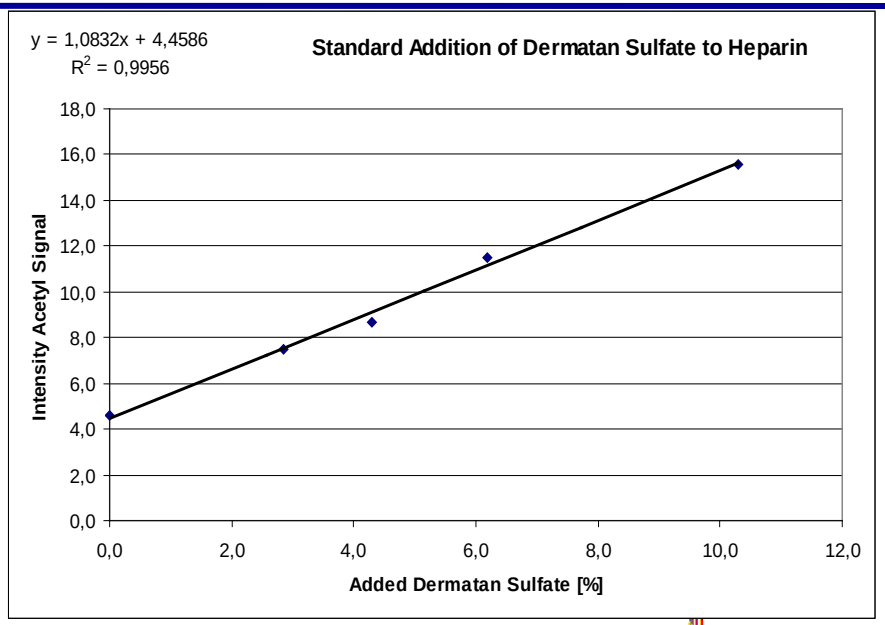


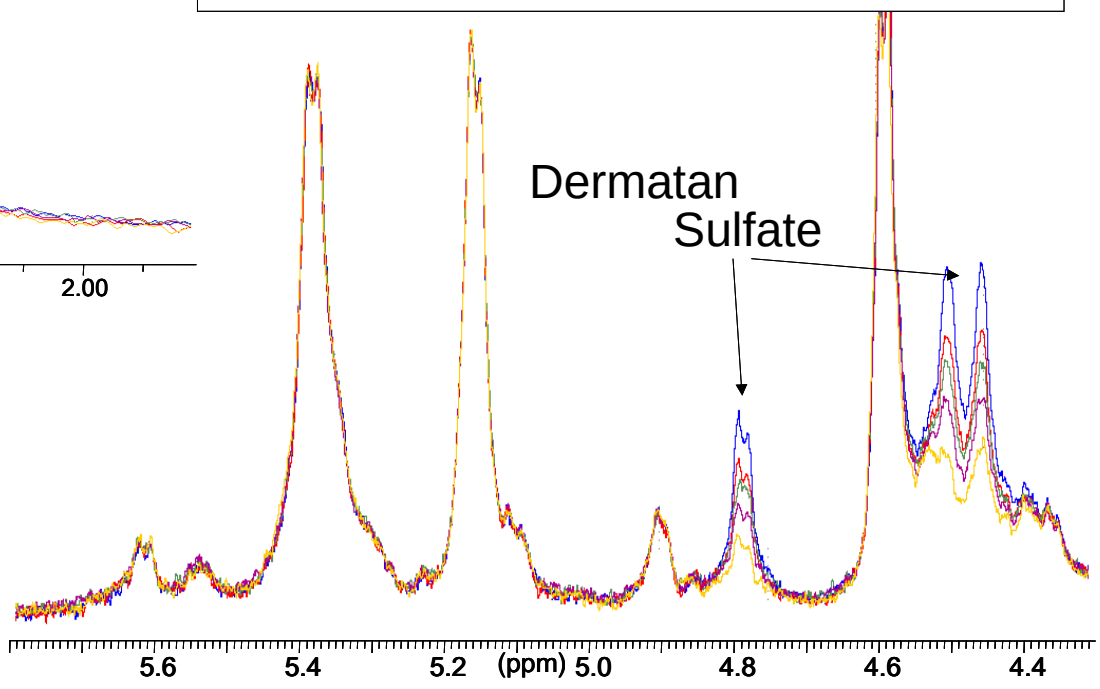
Beyer, Matz, Brinz, Rädler, Wolf, Norwig, Baumann, Alban, Holzgrabe, Eur. J. Pharm. Sci. 40 (2010) 297-304

Evaluation of Dermatan sulfate

Standard addition of DS to heparin



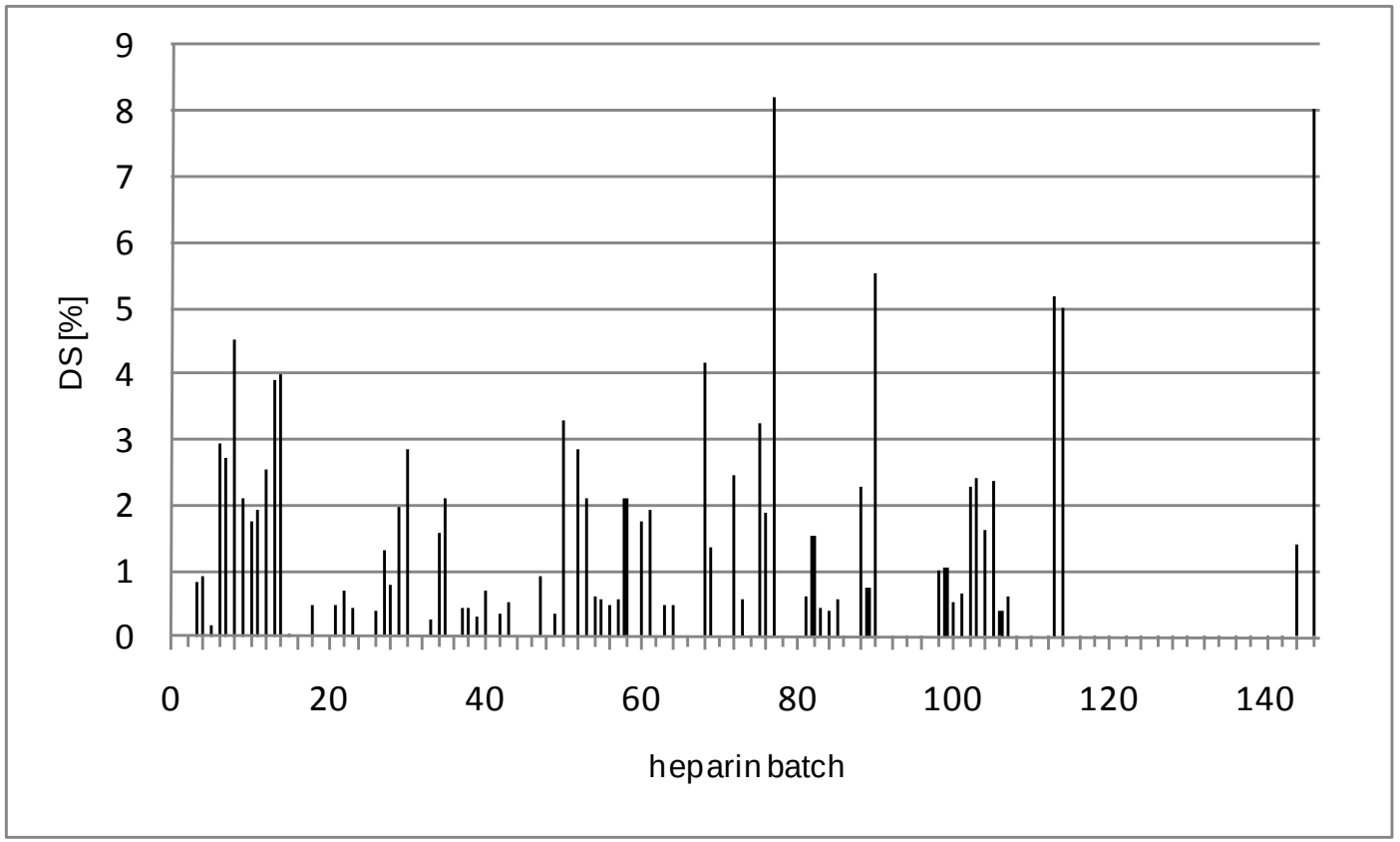




T. Beyer, B. Diehl, G. Randel, E. Humpfer, H. Schäfer, M. Spraul, C. Schollmayer, U. Holzgrabe, J. Pharm. Biomed. Anal. 48 (2008) 13-9

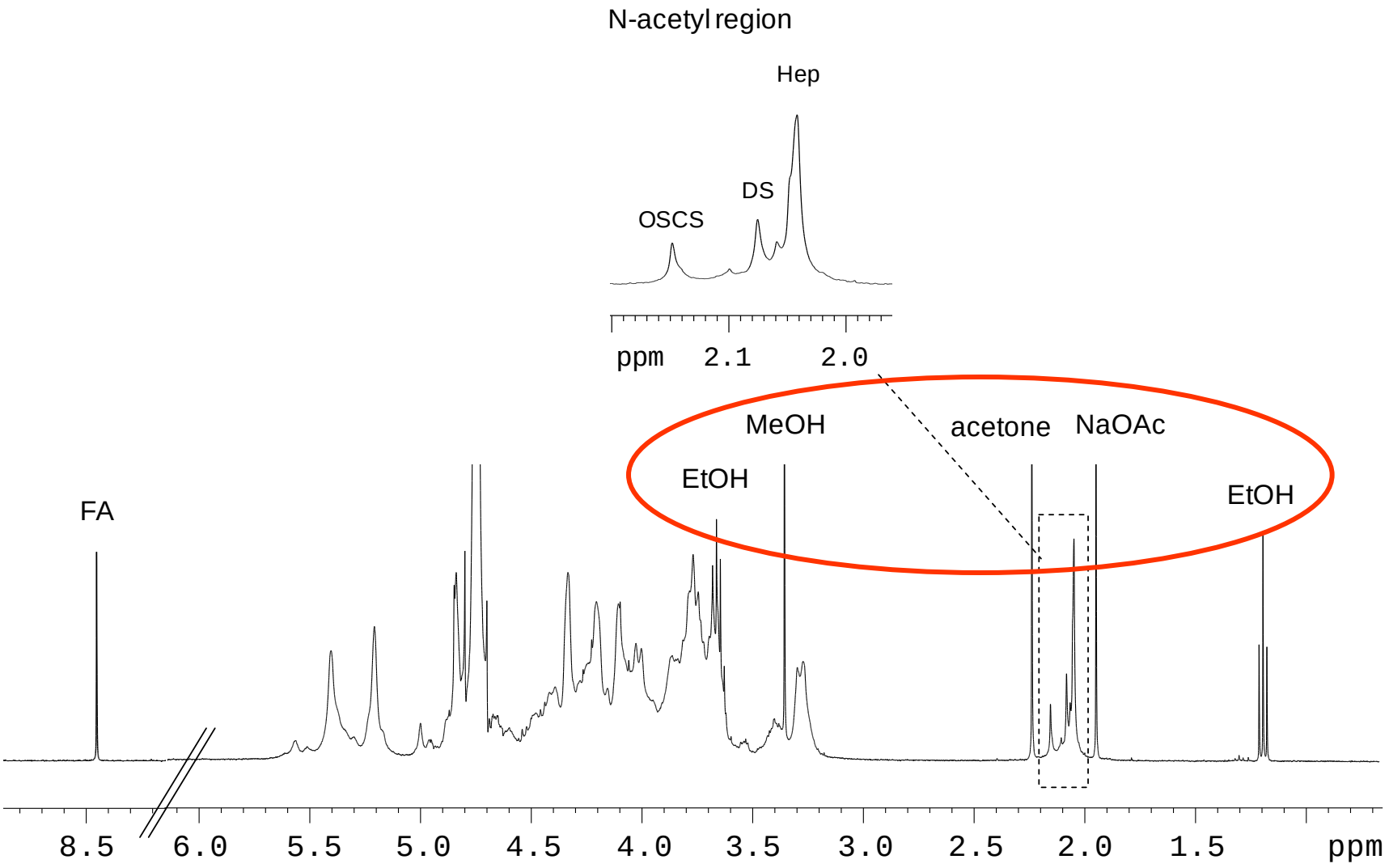
Heparin

Analysis of ~ 150 batches in Germany content of dermatan sulfate

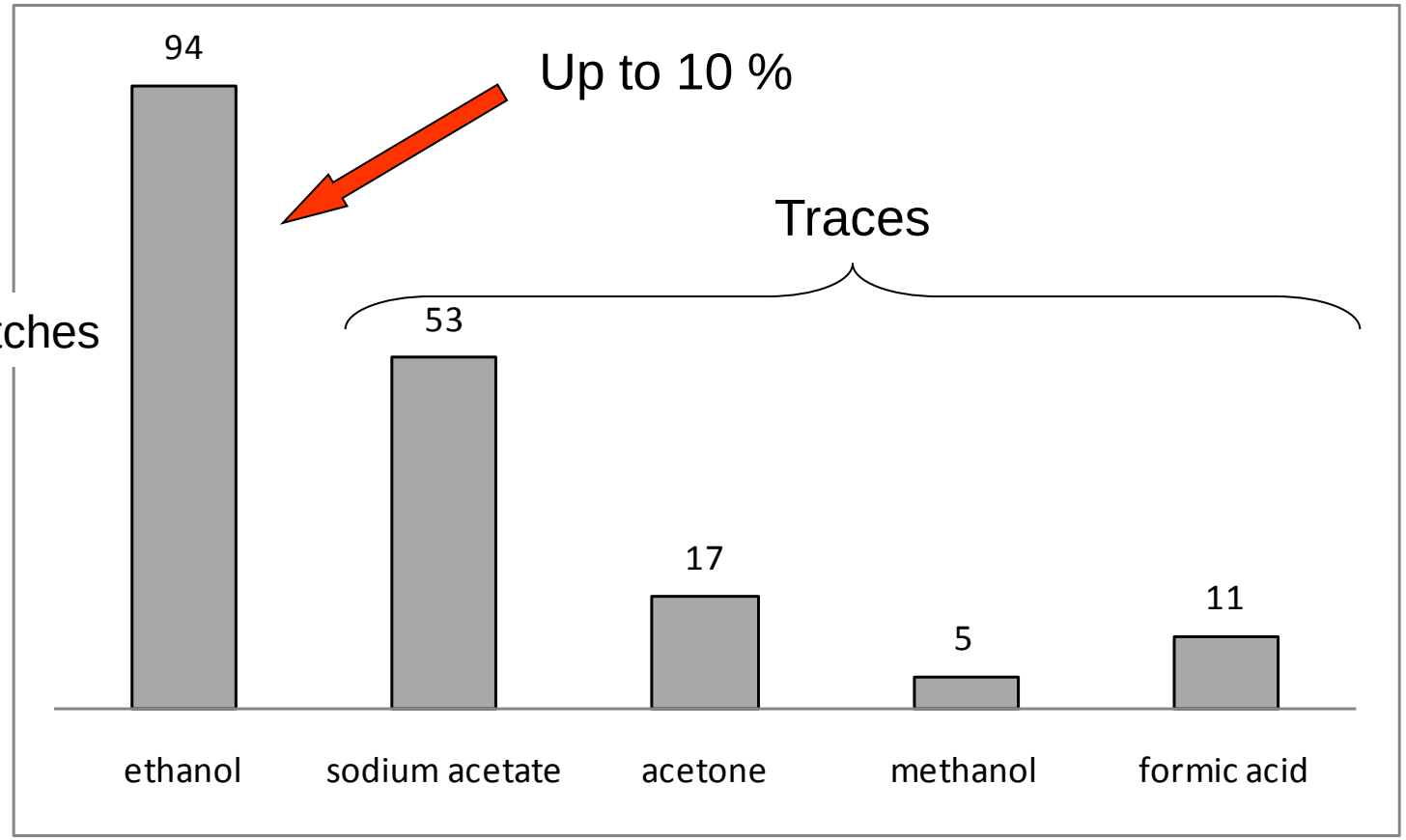


Beyer, Matz, Brinz, Rädler, Wolf, Norwig, Baumann, Alban, Holzgrabe, Eur. J. Pharm. Sci. 40 (2010) 297-304

Heparin - Residual Solvents

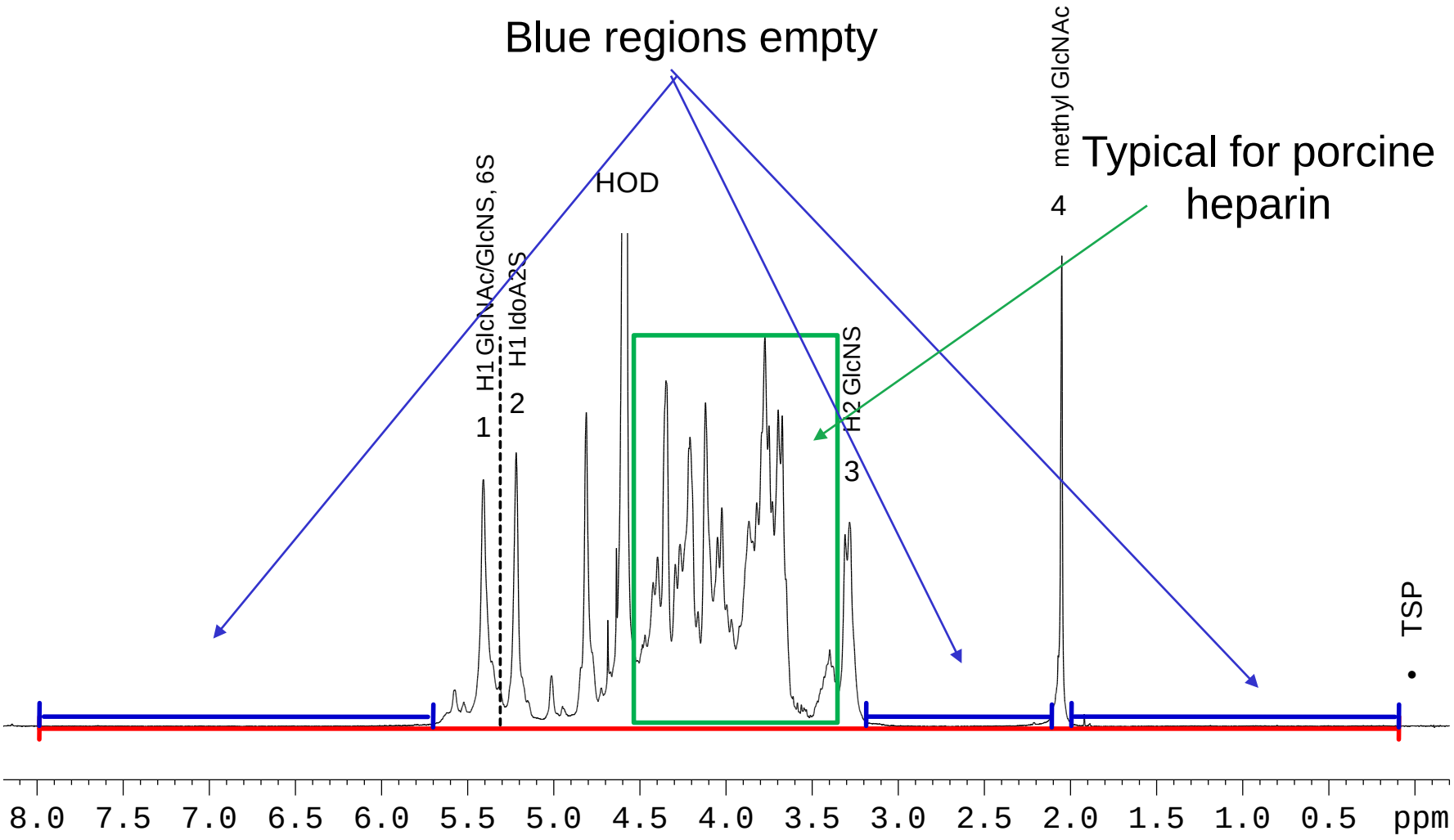


Analysis of ~ 150 batches in Germany content of residual solvents



Beyer, Matz, Brinz, Rädler, Wolf, Norwig, Baumann, Alban, Holzgrabe, Eur. J. Pharm. Sci. 40 (2010) 297-304

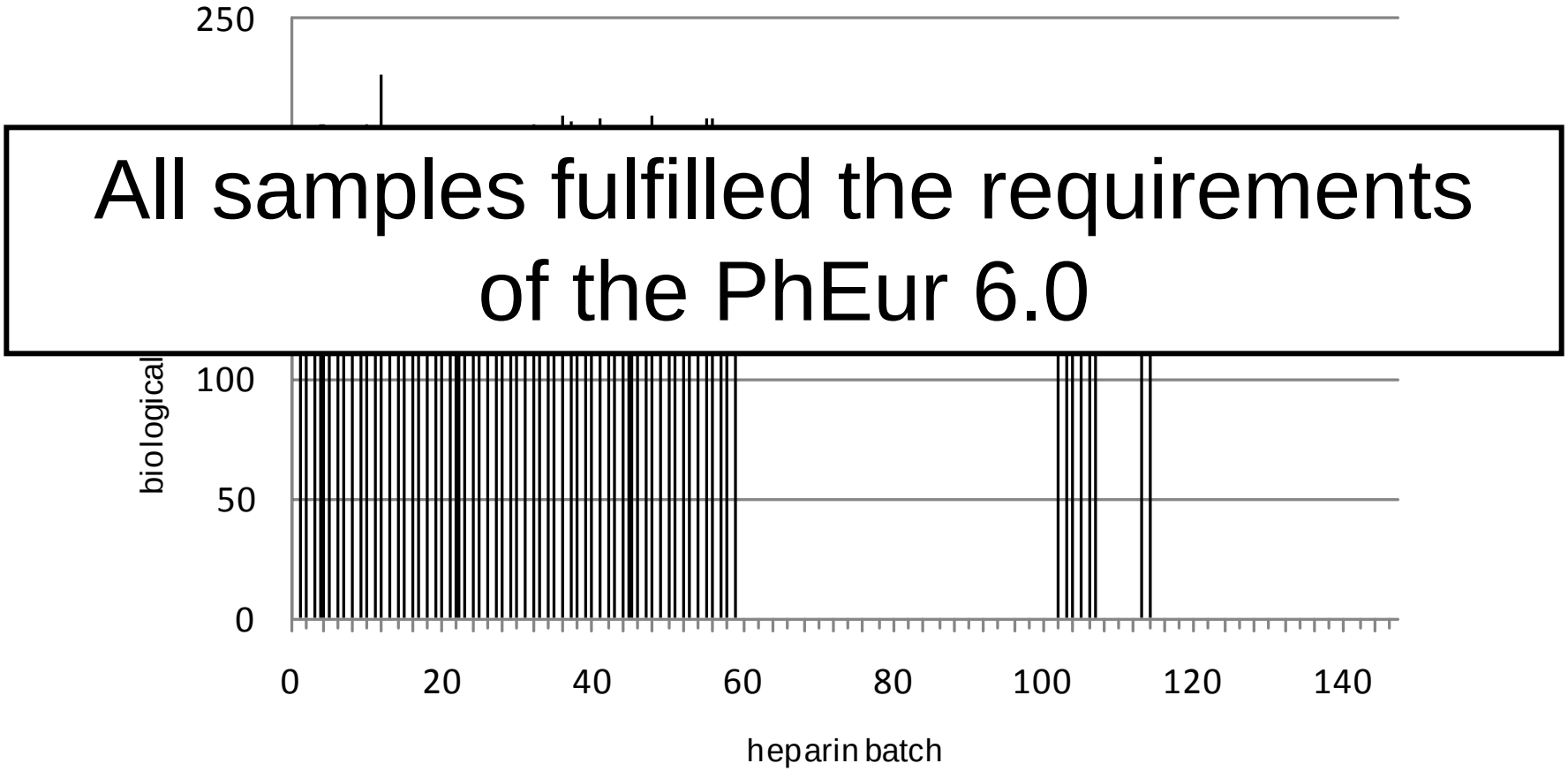
Heparin – PCA analysis



USP/PhEur: Identification test by means of NMR limits
OSCS, DS and residual solvents

Heparin – PCA analysis

Analysis of ~ 150 batches in Germany
Biological activity (sheep plasma clotting assay)

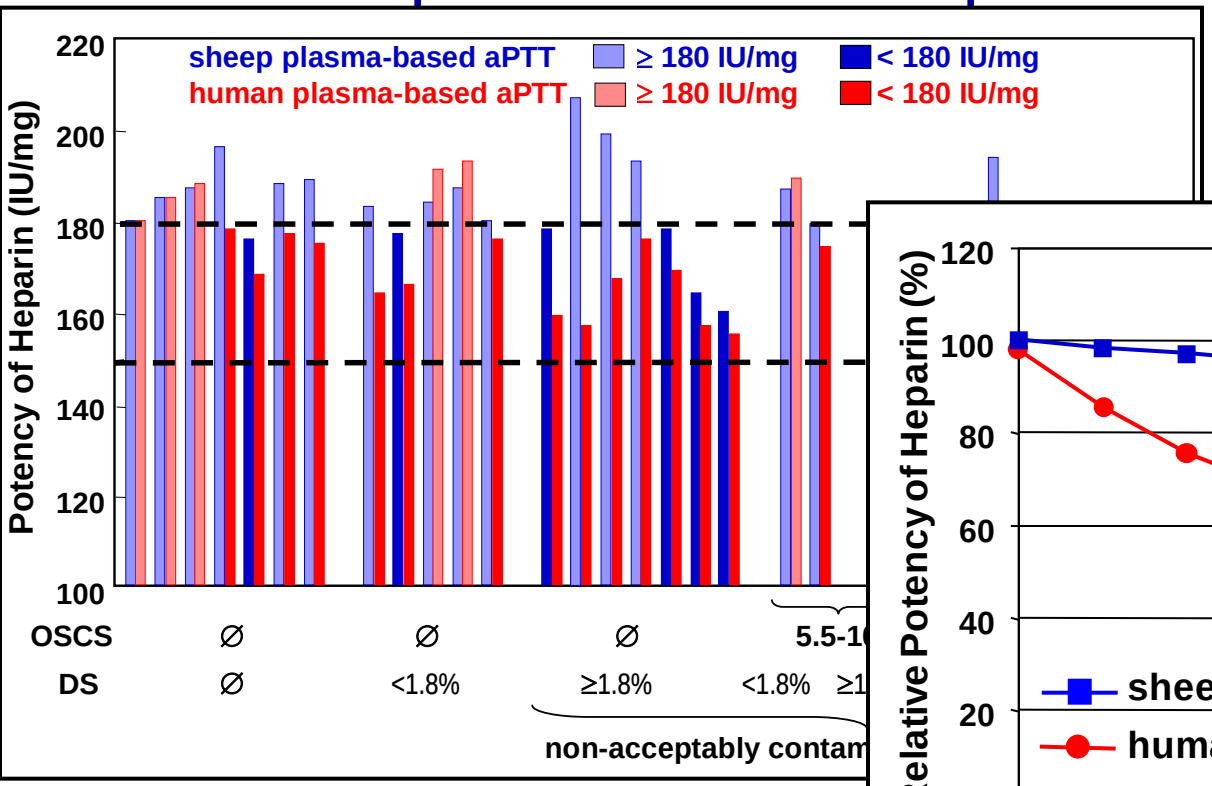


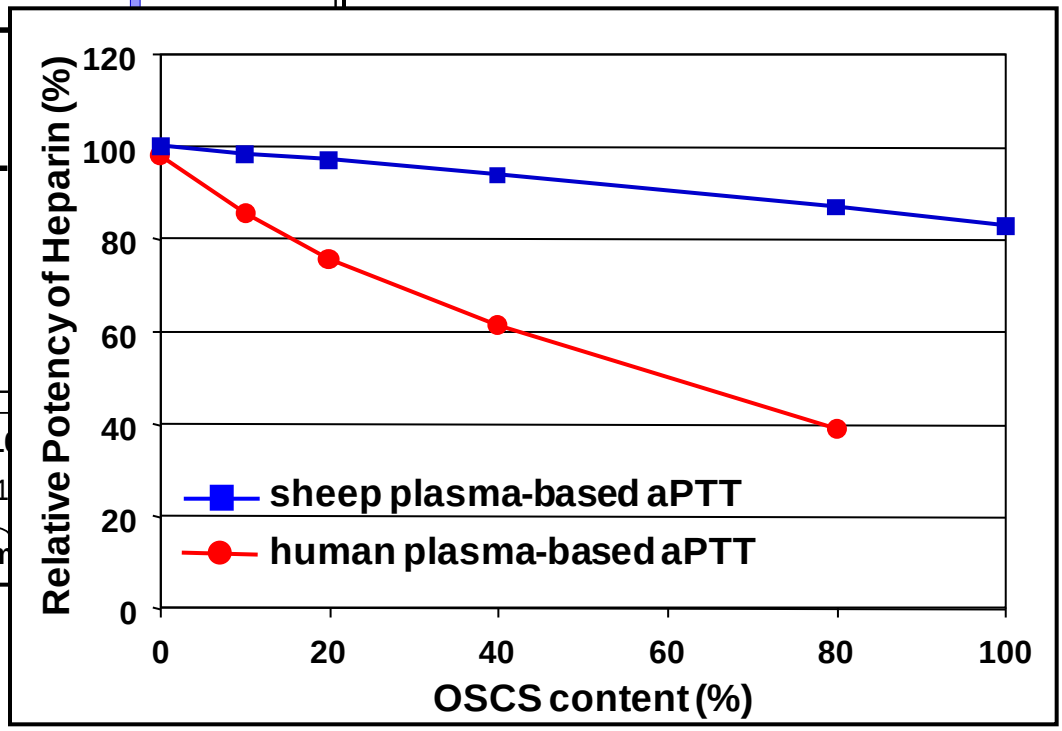
All samples fulfilled the requirements of the PhEur 6.0

Beyer, Matz, Brinz, Rädler, Wolf, Norwig, Baumann, Alban, Holzgrabe, Eur. J. Pharm. Sci. 40 (2010) 297-304

Heparin – PCA analysis

Analysis of ~ 150 batches in Germany
Sheep *versus* human plasma clotting assay





Alban, Lühn, Schiemann, Beyer, Norwig, Schilling, Rädler, Wolf, Matz, Holzgrabe,
Anal. Bioanal. Chem. 399 (2011) 605-620

Heparin

Guidance for Industry

Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact (CDER) Frank W. Perrella at 301-796-3265, (CVM) Dennis M. Bensley, Jr., at 240-276- 8268, or (CDRH) Jason Brookbank at 301-796-5770.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Veterinary Medicine (CVM)
Center for Devices and Radiological Health (CDRH)

February 2012
Current Good Manufacturing Practice (CGMP)

Heparin – Guidance for Industries

Recommendations:

- Test and confirm the species origin of crude heparin in each shipment before use in the manufacture or preparation of drugs (qualified method).
- Test for OSCS in crude heparin in each shipment before use in the manufacture or preparation of drugs.
- Know the identity and role of the actual manufacturer of crude heparin and any repackers and distributers.
- Employ the controls described in ICH Q7 to prevent the use of crude heparin containing OSCS.
- Reject for use, control, and properly dispose of any heparin found to contain any amount of OSCS or ruminant material contaminant.

Outline

- Definitions, Statistics, Overview of cases
- Heavy metals and contaminated dietary supplements
- Phthalate contamination
- The tryptophan case
- Heparin: OSCS, dermatan, porcine, etc.
- **What can be prevented by using a trace and track technology?**

Trace and Track technology

What can be prevented by using a trace and track technology?

2012 Cases:

Avastin (bevacizumab from Genentech/Roche) without any API (reported by the FDA February 2012): vials were packaged as Altuzan® (Turkish) wh or use in the US.

28th March 2012: Rich ed 120 packs of the faked Altuzan from Turkey, 38 packets were shipped directly to US, the rest was sold to another UK distributor who shipped them to US.

The counterfeits have moved through different networks of distributors: European regulators traced the packages through UK, Denmark, Switzerland, and the Middle East.

Trace and Track technology

What can be prevented by using a trace and track technology?

2012 Cases: WHO Alert 125

Isotab® 20 mg (isosorbide mononitrate) containing the antimalarial drug pyri[illegible] quantities (overdose) resulted in bone marr[illegible]leeding, which was seen in 450 patients.[illegible]s were reported by the Punjab Health Authority, Karachi, Pakistan, in February 2012.

Rog
Con

HPLC-UV – CAD – ELSD….

Raman

Near-IR

“In an era w economically motiv dulteration is
grow common, the scien nity
mu age in this ind of proactive strateg elp
protect the world´s upply.”

FT-IR

NMR

Terahertz

SFD ug 5, 2012): “… nufacturing
of fake drugs had become harde to detect…”

Thank you for attention!