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# A Changing Regulatory Environment.

Aginus A.W. Kalis
Executive Director of the MEB



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## Where do I come from?

- Intern, Pain Clinic
- Transplant Coordinator, Academic Medical Centre
- Medical Director, Solvay Pharma
- Head Healthcare Management, Achmea
- Director Public Health, Ministry of Health, Welfare and Sport
- Executive Director, Medicines Evaluation Board



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## Declaration of Interest

- Management Board EMeA
- Advisory Council TOPRA
- Board of Trustees TI-Pharma

- Board of “Cancer and Creative Arts”



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FT
FINANCIAL TIMES
18 September 2008

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Safety standards put under the microscope

News Analysis

Drugmakers in emerging economies are facing further intensive checks, says Andrew Jack

US concerns over hygiene spark ruling

Wave sees shares fall as much as 10%

The FDA is under strong domestic political pressure to address concerns about quality

Pharmaceuticals

FDA imposes Ranbaxy import ban

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Contaminated Heparin Associated with Adverse Clinical Events and Activation of the Contact System

Takashi Kei Kishimoto, Ph.D., Karthik Viswanathan, Ph.D., Tanmoy Ganguly, Ph.D., Subbiah Elankumaran, Ph.D., Sean Smith, B.S., Kevin Pelzer, Ph.D., Jonathan C. Lansing, Ph.D., Nammalwar Sriranganathan, Ph.D., Ganlin Zhao, M.D., Zoya Galcheva-Gargova, Ph.D., Ali Al-Hakim, Ph.D., Gregory Scott Bailey, B.S., Blair Fraser, Ph.D., Sucharita Roy, Ph.D., Thomas Rogers-C Lucinda Buhse, Ph.D., Mark Whary, Ph.D., James Fox, Ph.D., Mi Gerald J. Dal Pan, M.D., Zachary Shriver, Ph.D., Robert S. L Ganesh Venkataraman, Ph.D., K. Frank Austen, M.D., Janet W and Ram Sasisekharan, Ph.D.

ABSTRACT

BACKGROUND

There is an urgent need to determine whether oversulfated chondro a compound contaminating heparin supplies worldwide, is the c anaphylactoid reactions that have occurred after intravenous hepa in the United States and Germany.

emea European Medicines Agency
*Press office*

London, 6 June 2007
Doc. Ref. EMEA/251283/2007

PRESS RELEASE

**European Medicines Agency announces recall of Viracept**

The European Medicines Agency has been made aware in the evening of 5 June 2007 by Roche Registration Limited of a contamination with a harmful substance affecting the production of Viracept (nelfinavir), an antiretroviral medicine used to treat HIV-1 infected adults, adolescents and children of 3 years of age and older. As a consequence, the product is being recalled from the European Union markets, with immediate effect.

Roche has identified the presence of an unexpected contaminant ethyl mesylate (also known as methane sulfonic acid ethylester) in some batches of Viracept. Ethyl mesylate is a known genotoxic substance (harmful to DNA). The level of risk to patients resulting from this contamination is difficult to measure, and is currently under further evaluation.

As the contamination may have affected all strengths and presentations of Viracept, the company is performing a complete recall of the medicinal product. All packs of Viracept currently available on the market, including packs that patients may have at home, will need to be returned to the pharmacy.





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From The Times
August 20, 2008

## Drug trials in India under investigation after 49 babies die at leading hospital

The deaths occurred over a period of 30 months at the All India Institute of Medical Sciences public hospital in Delhi





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Last Updated: Wednesday, 15 March 2006, 22:37 GMT

## Two drug trial men critically ill

**Two men remain critically ill and four others are in a serious condition after suffering a violent reaction while taking part in a clinical drugs trial.**

The six are being treated at Northwick Park hospital

All are still in intensive care in Northwick Park Hospital, north-west London, after falling ill on Monday.

Myfanwy Marshall told BBC News her boyfriend's body was badly swollen and she had been told he could die.

One of the drugs companies involved in the trial said it has apologised to the families of the men.

But relatives are said to be unhappy with the information given from the firm behind the anti-inflammatory drug.

The families had been given "mixed messages" during two meetings with pharmaceutical company TeGenero AG, which manufactures the drug and Parexel, which ran the trial, it was claimed.



DrugResearcher.com — Breaking News on Drug Discovery

DrugResearcher › Research management › Northwick trial tragedy: scientists reveal how 'cytokine storm' started

News headlines | Research management

## Northwick trial tragedy: scientists reveal how 'cytokine storm' started

By Mike Nagle

29-Jan-2007 - **Scientists have revealed a possible reason why the Northwick Park clinical trial of a drug designed to stimulate the immune system instead led to multiple organ failure in the human volunteers.**

Scientists from the Department of Immunology at Imperial College London and the Babraham Institute, showed that using TGN1412 to stimulate white blood cells, which mediate the immune response, can have an adverse effect if the immune cells have been activated or altered by infection in the past.

The research finally sheds light on the Northwick puzzle, which scientists have been at a loss to explain until now, and the information could be used to prevent further clinical trial tragedies in the future. The severe negative effects observed in the six human volunteers were especially unexpected because no adverse were seen in previous studies on monkeys even though they were given a dose 500 times greater than the human volunteers.

Instead of subtly 're-tuning' the immune system, as developer TeGenero hoped, TGN1412 induced a so called 'cytokine storm'; the immune system was sent into overdrive and attacked healthy organs with tragic results. However, key questions remained: what started the storm and why wasn't it observed in preclinical research?

The scientists discovered that when they stimulated CD28 on these previously activated 'memory' T cells, they migrated from the blood stream into organs where there was no infection and caused significant tissue damage.

*"Our research suggests that this is because the human subjects' memory T-cells lost their sense of direction and started migrating into several areas of the body where they were not supposed to go, and caused damage,"* said Dr Frederica Marelli-Berg from Imperial College London.





News Focus

After the discovery that several popular medicines may have harmed tens of thousands of people, experts are hunting for better ways to monitor drugs on the market

## Gaps in the Safety Net

For those who trust government-approved drugs, 2004 was not a banner year. Merck, the maker of the anti-inflammatory medicine Vioxx, pulled the drug off the global market in September after a clinical trial linked it to heart attacks and strokes. In October, U.S. regulators concluded that a class of anti-depressants can trigger suicidal thoughts in children and stepped up warnings of this danger. In December, studies of Celebrex, another arthritis medication, pointed to more cardiac risks. Just 5 days before Christmas, scientists running an Alzheimer's prevention study announced that Aleve, approved as a nonprescription painkiller in 1991, may also trigger heart problems.

These cases all involved drugs that had gone through extensive safety testing and had been on the market for years. And they raised disturbing questions: Should public authorities like the U.S. Food and Drug Administra-

Since the Vioxx debacle, officials running postmarketing surveillance systems are considering how they might do better. The uncomfortable truth, some say, is that all such systems have gaps. Several nations and the European Union (E.U.) boast aggressive surveillance systems, but many are new and have not been rigorously tested. "Everybody's in bad shape here," says Bert Leufkens, a pharmacoepidemiologist at the University of

**Risk tolerance**

Forty years ago, European countries seemed relatively relaxed about drug approvals in contrast to FDA, which had earned a reputation for caution. Europe released thalidomide onto the market in the late 1950s, for example, and left it there for years. But an FDA reviewer spotted potential problems; she declined to let thalidomide through, and it was not approved.

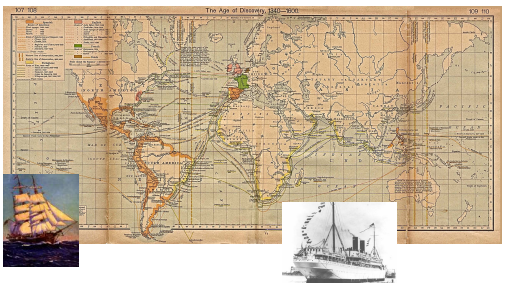
Today, the roles are often reversed. FDA is frequently the first to approve drugs. The FDA staff is paid in part by "user fees" from regulated companies. Industry and patient groups lobby for speedy decisions, and FDA now turns some applications around in 6 months.

FDA has allowed greater risks in recent years than some other regulatory agencies, according to observers such as Lucien Abenhaim, a pharmacoepidemiologist at the University of Paris and McGill Univer-





## *Times...*



## … are changing



## Challenges (1)

- Quality standards (GCP + GMP….)
- Ethical aspects
- Counterfeit



## Challenges (2)

- Converging technologies
- Development problems
- EU regulation
- Regulatory Science



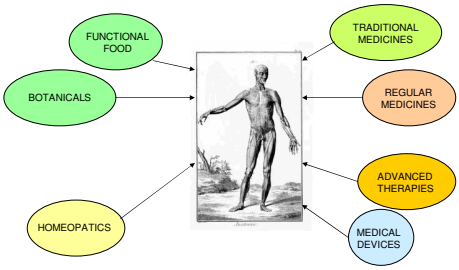
The field is broader than just pharmaceuticals.

There is a host of products that are used in health care and for humans which are to a smaller or greater extent “adjacent” to pharmaceuticals:

- medical devices
- human tissues
- advanced therapy products
- cosmetics
- food supplements and functional foods



## Range of products






There is a certain ***convergence*** in these fields.

Transparency and coherence in regulation across product categories are necessary.

In addition, it should be clear to any user, producer or other stakeholder, under what category a product resorts.

## Blurring of 'traditional' boundaries

Which products cross the 'traditional' border between drugs and devices?

- Borderline Products
- Combination products



## Borderline products

- Osmotic laxans
- Cooling gel with menthol
- Active charcoal
- Heparin solution for rinsing catheters
- "Cosmetic" products, e.g. Botox / tooth whiteners
- Electronic sigaret

Borderline discussions could be considered as 'indicator' of coherence between definitions



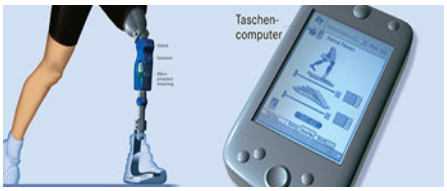
## Super Smoker:

*pharmaceutical?*
*consumer product?*
*medical device?*



## Converging Technologies: Artificial Limbs

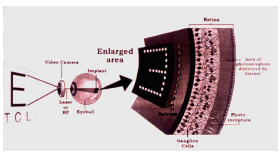
Rheoknee[R]: joint filled with fluid with nanoparticles, with a 'memory'





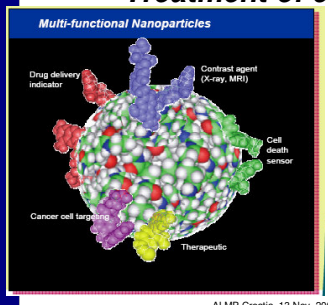

## Converging Technologies: Retinal prosthesis

Second Sight[R]: array of electrodes, attached to the retina and used in conjunction with an external camera and video processing system.






## Converging Technologies: Treatment of cancer

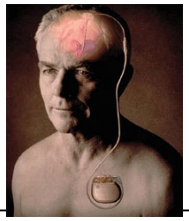



- Targeting
- Imaging
- Therapy
- Monitoring

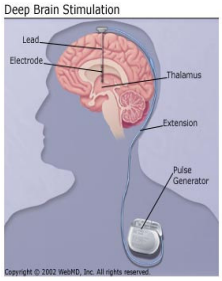
in one molecule

## Converging Technologies: Deep Brain Stimulation

Parkinson's Disease
Syndrome of Gilles de la Tourette



Deep Brain Stimulation



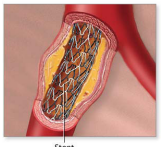



## Implantable materials

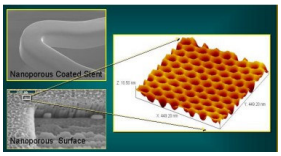
***Stent coatings***

– Nanoporous alumina and hydroxyapatite coatings increase biocompatibility and thus efficient stenting – *development phase*
- e.g. AlCove Surface GmbH, Germany
- Debiotech SA, Switzerland

– Similar coatings carrying drugs for drug-eluting stents – *development phase*
- MIV Therapeutics Inc, Canada




adam.com






## Implantation for reconstruction



## Convergence of technologies

- Convergence of technologies blurs the traditional boundaries between pharmaceuticals and the "adjacent" product categories
- Cooperation and coordination with other sectors will be mandatory and challenging
- Even more challenging will be to aim for coordination and harmonization at a global level



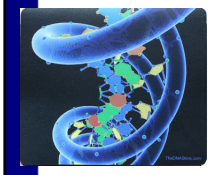
## *Advanced therapy products*

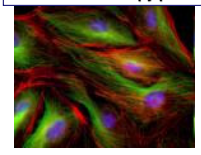
Combined ATP

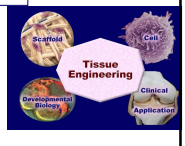
Gene therapy products

Tissue engineered products

Somatic cell therapy products








Source: EMEA



## Development problems

- Predicted “revolution in medicine” has failed to materialize
- High hopes in advanced therapies have not yet been fulfilled
- Industry always looking for “blockbusters”
- BUT: Less New Chemical Entities



## Setting the agenda on regulatory hurdles



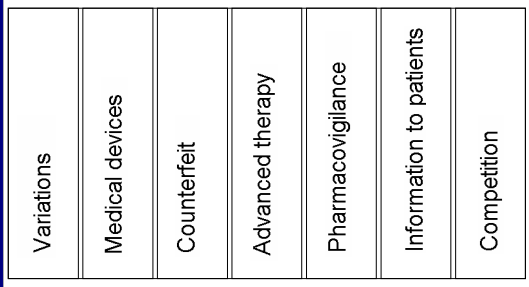

## Consultations

In 2007, the EC (3 different DGs) has conducted 7 consultations:

- Variations
- Medical devices
- Counterfeit
- Advanced therapy
- Pharmacovigilance
- Information to patients
- Competition

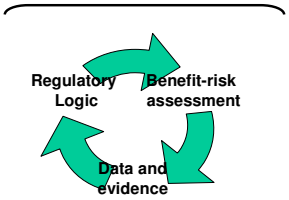


## There are no segments






## Regulatory governance



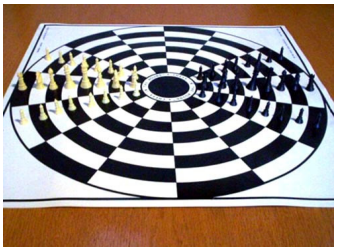

## Regulatory learning



## Regulatory Science

- Make more boundaries or take them away? Be strict or flexible? (e.g. regarding orphan drugs)
- Lowering our standards leads to which consequences?
- What guarantees does a Risk Management Plan give?

## The way ahead…





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