Past, Present and Future of the Pharmaceutical Sciences. A Personal View

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prof. Emeritus,

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PHARMA 2030 – CURRENT AND FUTURE CHALLENGES

University of Innsbruck, Austria | 20 – 22 April 2017

A Joint Meeting of the Austrian Pharmaceutical Society (ÖPhG) and the Swiss Academy of Pharmaceutical Sciences (SAPhS)

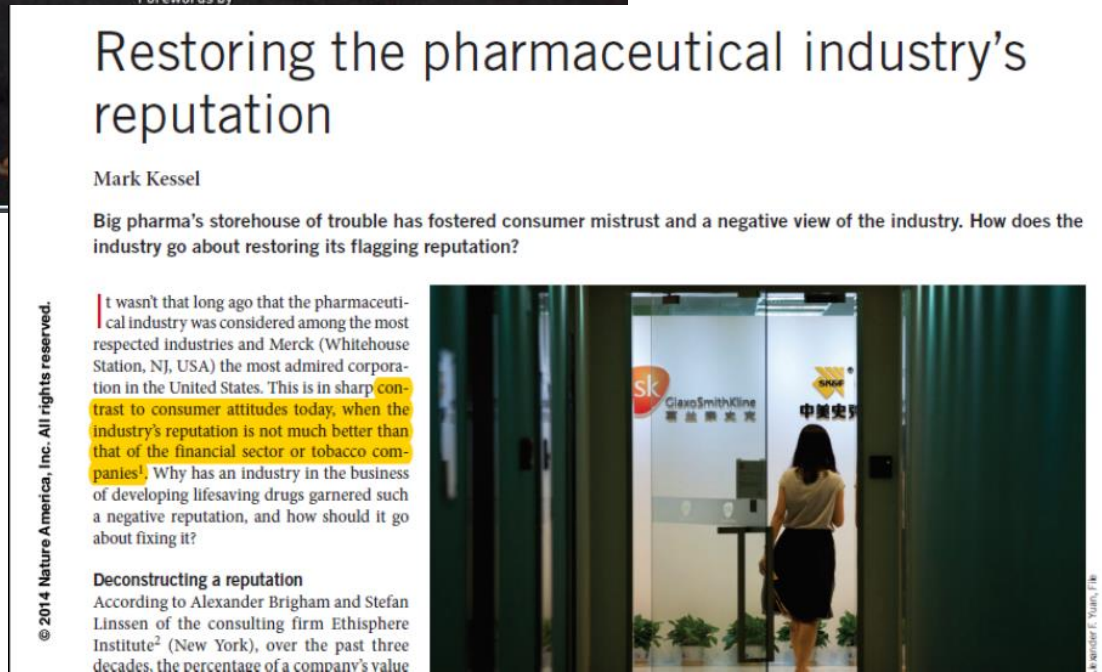
What to discuss? A personal choice

- *Present state and Past performance? Impact of the Pharmaceutical Sciences*
- Did we lose something? Do we never learn? Are we too naive?
- Future: scenarios
- Emerging areas/Blurring borderlines/Science business models

General challenges for Pharma

And consequences…… for pharmaceutical scientists

Do you dare to tell guests at a birthday party that you work for pharma?



Restoring the pharmaceutical industry's reputation

Mark Kessel

Big pharma's storehouse of trouble has fostered consumer mistrust and a negative view of the industry. How does the industry go about restoring its flagging reputation?

It wasn't that long ago that the pharmaceutical industry was considered among the most respected industries and Merck (Whitehouse Station, NJ, USA) the most admired corporation in the United States. This is in sharp contrast to consumer attitudes today, when the industry's reputation is not much better than that of the financial sector or tobacco companies[1]. Why has an industry in the business of developing lifesaving drugs garnered such a negative reputation, and how should it go about fixing it?

Deconstructing a reputation

According to Alexander Brigham and Stefan Linssen of the consulting firm Ethisphere Institute[2] (New York), over the past three decades, the percentage of a company's value

Sanofi epilepsy drug led to serious birth defects in thousands of children

HARRIET AGNEW — PARIS

A drug made by Sanofi to treat epilepsy and bipolar disorders that was given to pregnant mothers resulted in up to 4,100 French children being born with significant birth defects, the French medical authority said yesterday.

During the 50 years from 1967-2016, between 2,150 and 4,100 children were born with at least one serious congenital disorder, after being exposed in the womb to a drug called valproate, according to a preliminary study from ANSM, France's drug regulator.

It was the first official estimate of the number of cases of birth defects linked to valproate in France. The drug has been sold in a number of global markets, including the US, China and the UK.

"The study confirms the highly teratogenic [capable of causing birth defects] nature of valproate," Mahmoud Zureik, ANSM's scientific director and co-author of the report, told AFP news agency. "The figure of about 3,000 severe malformations is very high."

The case has echoes of the thalidomide scandal — one of the darkest cases in pharmaceutical history — in which an estimated 10,000 children worldwide were born with malformed limbs between 1956 and 1963. Drugmakers were among those sued in the long battle to determine responsibility.

Sanofi, which from 2011 had warned the drug should not be used during pregnancy, said: "We are aware of the painful situations faced by families whose children have problems that may be related to their mother's treatment of anti-epileptic drugs during pregnancy."

It added that as scientific knowledge on the risks associated with the use of sodium valproate, particularly during pregnancy, has increased it has been transparent with health authorities.

Valproate, introduced in France in 1967, is sold by Sanofi under the brand Depakine to treat epilepsy and as Depakote or Depamide for bipolar disorders.

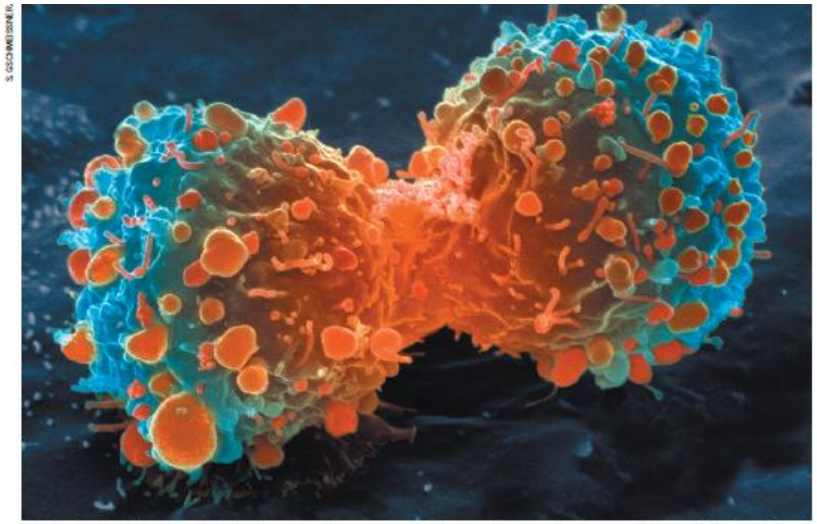
The study found that the risk of major birth defects in children whose mother was treated with valproate for epilepsy was four times higher than the general population, and twice as high when the mother was treated with the same drug for a bipolar disorder. ANSM said this was because women treated for bipolar disorder were less exposed to the drug.

The US Food and Drug Administration warned healthcare professionals and women in 2013 that valproate sodium and related products, valproic acid and divalproex sodium, should not be taken during pregnancy.

FT 21 April 2017

AND WHAT ABOUT ACADEMIA?

IVORY TOWERS FALLING DOWN



Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

Raise standards for preclinical cancer research

C. Glenn Begley and Lee M. Ellis propose how methods, publications and incentives must change if patients are to benefit.

29 MARCH 2012 | VOL 483 | NATURE | 531

…… Nevertheless, scientific findings were confirmed in only 6 (11%) cases ……

Believe it or not: how much can we rely on published data on potential drug targets?

Florian Prinz, Thomas Schlange and Khusru Asadullah

NATURE REVIEWS | DRUG DISCOVERY

house findings (FIG. 1c). In almost two-thirds of the projects, there were inconsistencies between published data and in-house data that either considerably prolonged the duration of the target validation process or, in most cases, resulted in termination of the projects because the evidence that was generated for the therapeutic hypothesis was insufficient to justify further investments into these projects.

Can we do something about that?

Report commissioned by the Board of Pharmaceutical Sciences,
FIP, the International Pharmaceutical Federation

Impact of the Pharmaceutical Sciences on Health Care in the last 50 years

J. Pharm Sci 101: 4975-4999, 2012

1966

FIP 2012

2016

PERSPECTIVES

Impact of the Pharmaceutical Sciences on Health Care: A Reflection over the Past 50 Years

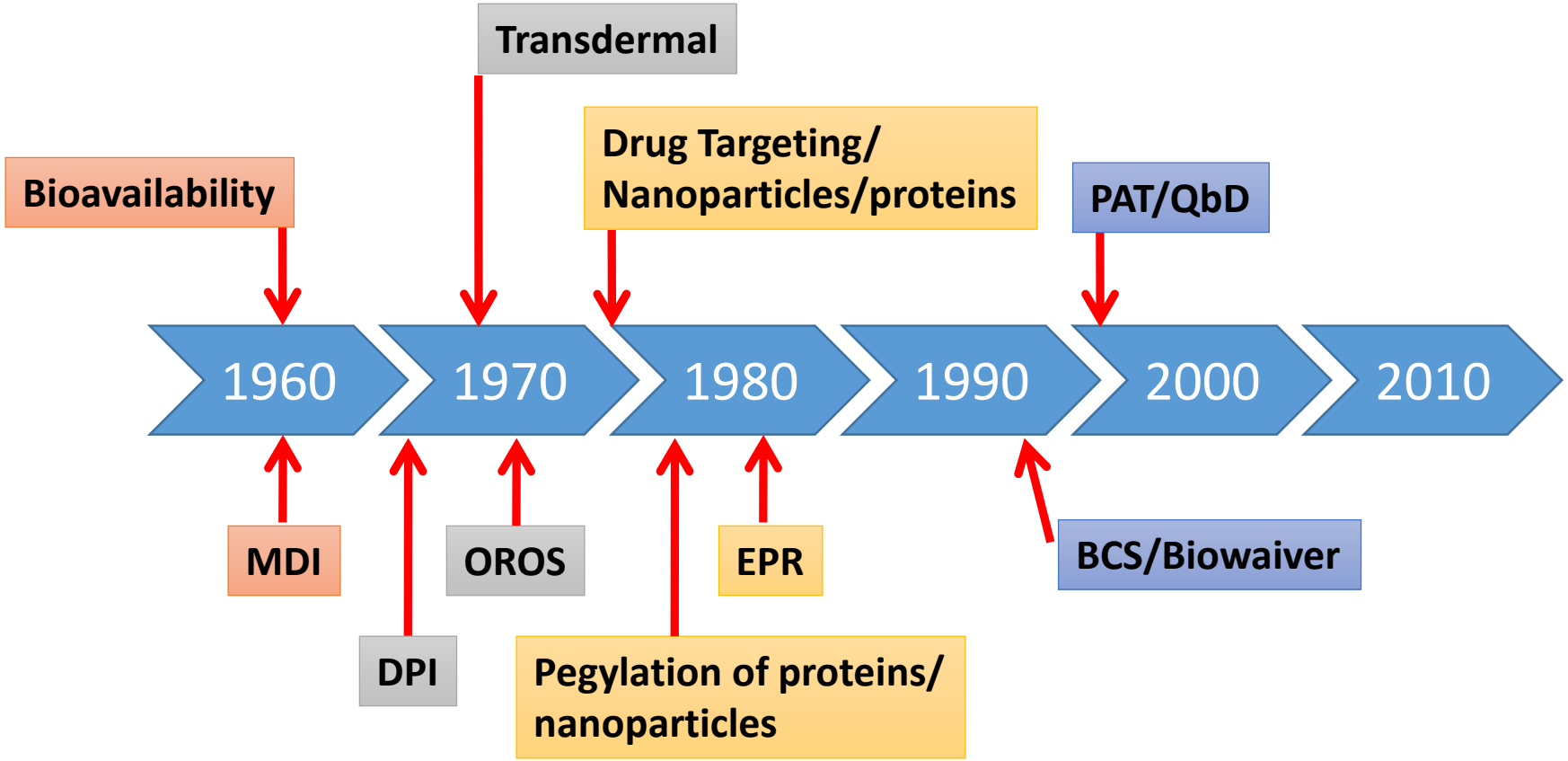
MALCOLM ROWLAND,[1,2] CHRISTIAN R. NOE,[3] DENNIS A. SMITH,[4,5] G. T. TUCKER,[6,7] DAAN J. A. CROMMELIN,[8] CARL C. PECK,[2] MARIO L. ROCCI Jr.,[9] LUC BESANÇON,[10] VINOD P. SHAH[10]

- Divided into six sections :
  - ❑ **Drug discovery**
  - ❑ **ADME (absorption, distribution, metabolism, and excretion)**
  - ❑ **Pharmacokinetics and pharmacodynamics**
  - ❑ **Drug formulation (Pharmaceutics)**
  - ❑ **Drug regulation**
  - ❑ **Drug utilization**

  each describing key contributions that have been made in the progression of medicines, from conception to use.
- Common thread: application of translational science to improvement of drug discovery, development and therapy.

Courtesy of prof. Malcolm Rowland

Formulation Sciences: Timeline of introduction of key concepts and developments



MDI = metered dose inhaler

DPI = Dry powder inhalation

OROS = osmotic release oral system

EPR = enhanced permeability and retention effect

PAT/QbD = process analytical technology

Quality by design

Contributions of pharmaceutical sciences during past 50 years

- From description to mechanistic prediction.
- Targeting for specificity of action.
- Building druggability qualities into design.
- Optimising drugs, products, and dosage regimens for patients through PK/PD modeling.
- Building quality and reproducibility into drug delivery systems and products.
- Ensuring regulation reflects scientific developments.
- Delivering better medicines, including generics, to patients.

J. Pharm Sci 101: 4975-4999, 2012

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Insulin and the dog
and how to move fast!

Banting and Best

Courtesy of Alexander Florence

Those were the days.....
Publication early 1922

Nobel prize Banting 1923

Ethics: ‘Tempora mutantur et nos mutamur in illis’

INSULIN BY THE SKIN AND MOUTH.

To the Editor of THE LANCET.

SIR,—With reference to the annotation with this heading in your issue of Feb. 23rd I should like to ask whether insulin has ever been tried by the rectum. If not, perhaps readers who are in a position to do so would try this route, giving watery or oily suspensions of small bulk after an evacuation of the lower bowel, and publishing their results.

I am, Sir, yours faithfully,

H. H. KING,
Major, I.M.S.

Central Research Institute, Kasauli,
March 20th, 1924.

Oral/rectal administration of insulin was and is a challenge

INSULIN BY THE SKIN AND MOUTH.

To the Editor of THE LANCET.

SIR,—Major H. H. King will find in THE LANCET of Oct. 6th, 1923 (p. 777), that a negative result was obtained by my colleagues and myself after administering insulin per rectum in a case of diabetes. The necessary control experiments were carried out.

I am, Sir, yours faithfully,

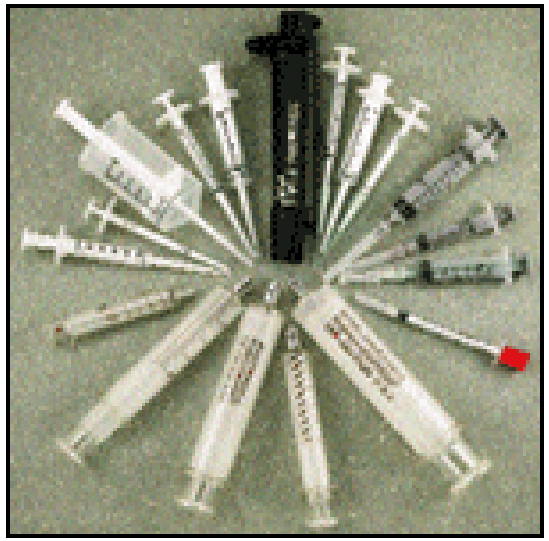
E. P. POULTON.

London, W., April 15th, 1924.

Courtesy of Alexander Florence

Delivery of Biologicals:

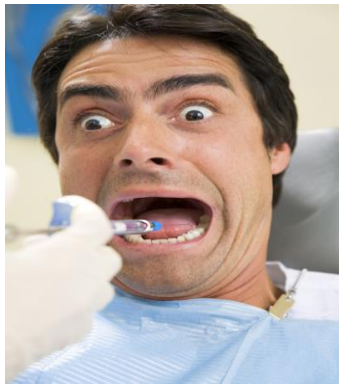
Do we have to stick to the needle?



Patients

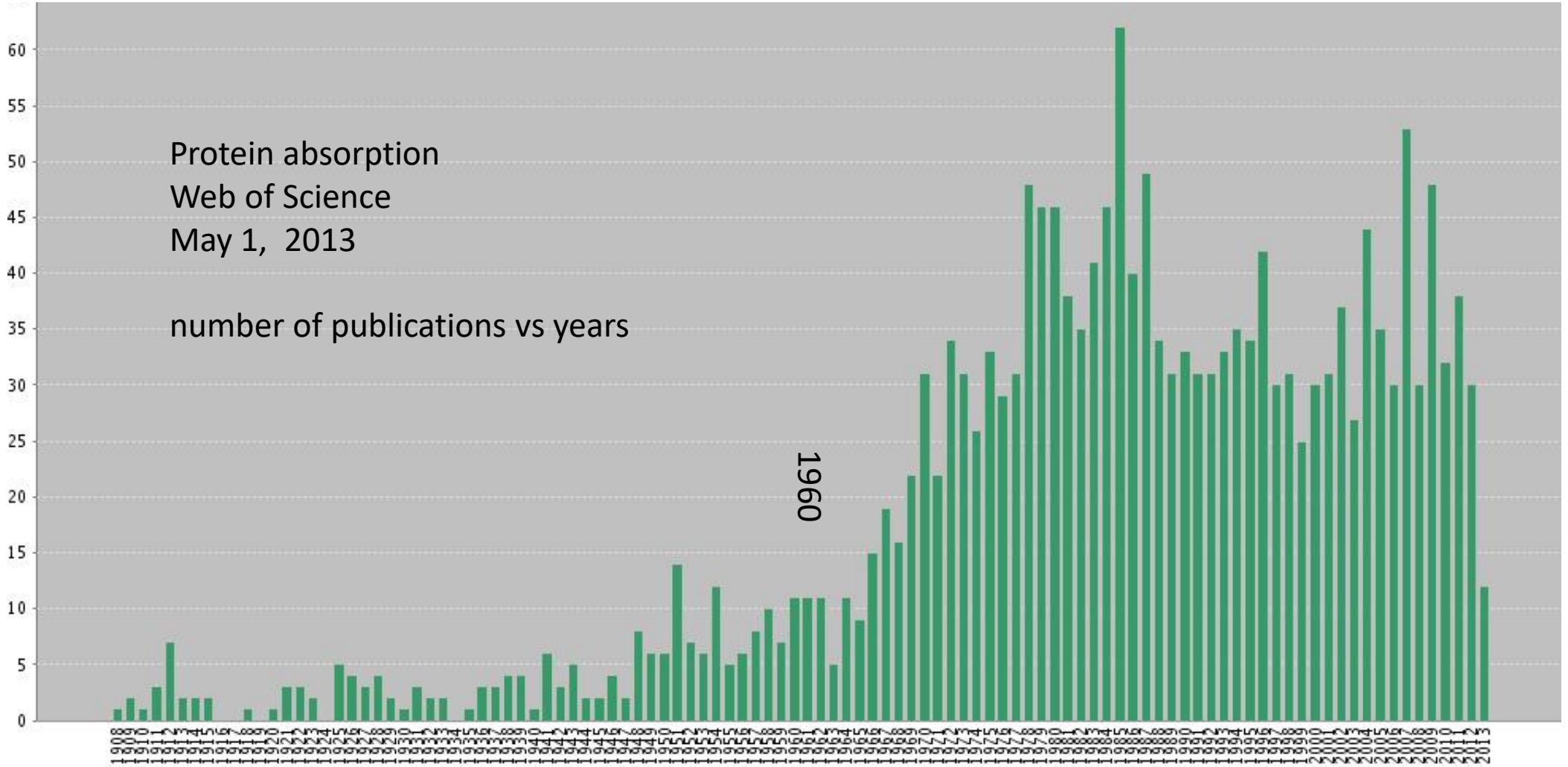
-Needlephobia-

Needle phobia is a recently defined medical condition that affects **at least 10% of the population**. The etiology of needle phobia lies in an inherited vasovagal reflex of shock, triggered by needle puncture.

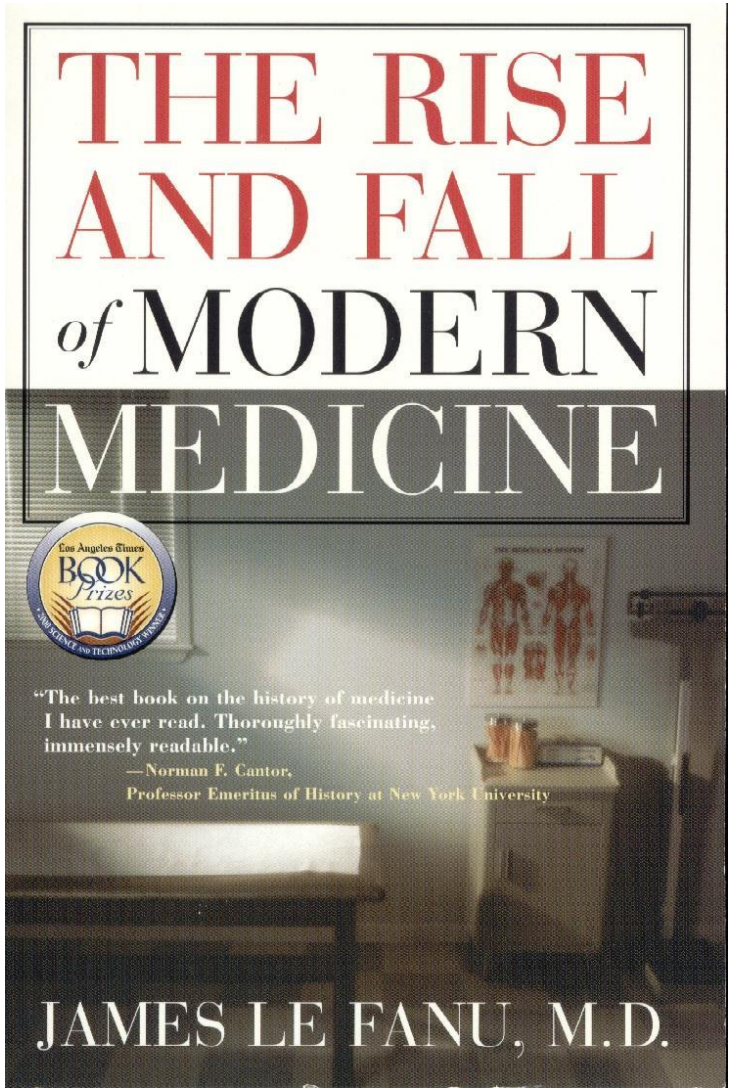


- Victims of needle phobia typically experience a temporary anticipatory tachycardia and hypertension, which on needle insertion turns into a state of shock - bradycardia and hypotension, accompanied by pallor, diaphoresis, tinnitus, vaso-vagal syncope (fainting), and sometimes cardiac arrest and death.
- Because persons with needle phobia typically avoid medical care, this condition is a **significant** impediment in the health care system.
- That‘s why a confirmed needlephobia is a reason for health insurances to incure the expenses of needlefree devices.

From Dr. Dieter Gothier, LTS symposium, 2012



After all those years, still no orally administered protein medicine



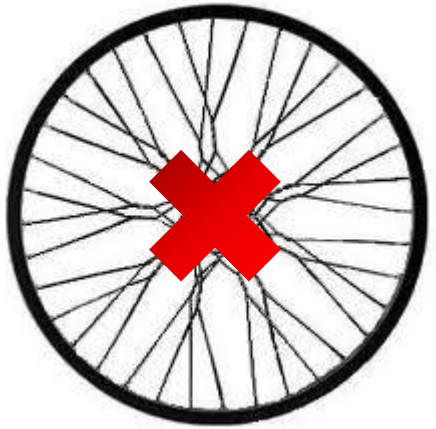
PART 1: THE RISE

PART 2: THE END OF THE AGE OF OPTIMISM

PART 3: THE FALL

Did we lose something?

- The **precautionary** principle or precautionary approach states if an action or policy has a suspected risk of causing harm to the public or to the environment, in the absence of scientific consensus that the action or policy is harmful, the burden of proof that it is *not* harmful falls on those taking an action.



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- *Future: scenarios*
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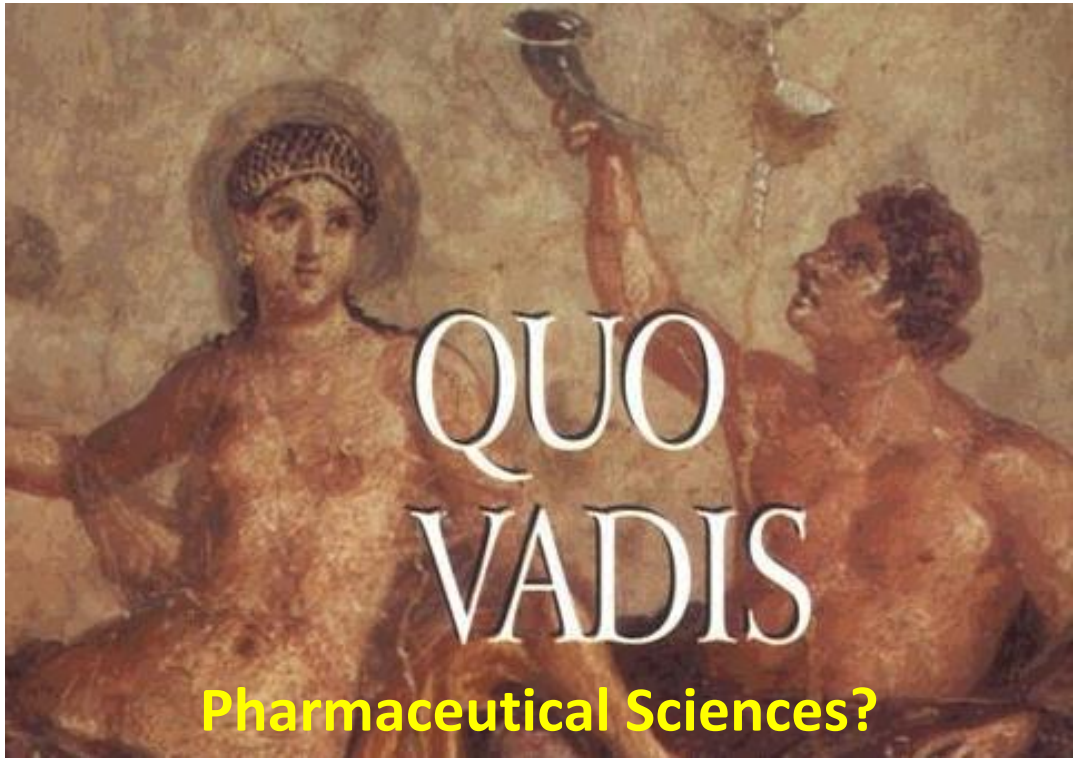
Pharmaceutical Sciences in 202?

A scenario analysis

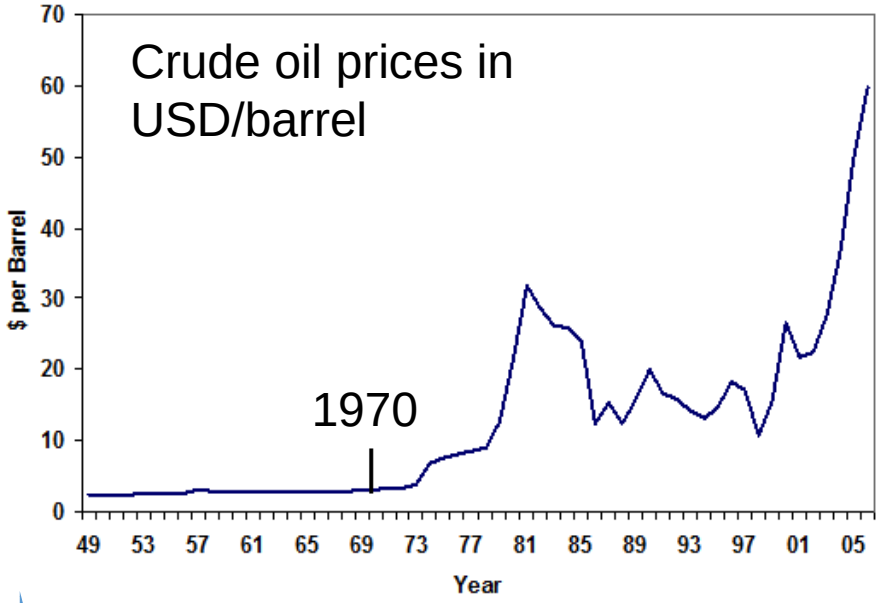
NATURE REVIEWS | DRUG DISCOVERY VOLUME 9 | FEBRUARY 2010 | 99

Daan Crommelin, Pieter Stolk, Bert Leufkens


QUO
VADIS
Pharmaceutical Sciences?

Applications in the private sector

Pierre Wack
(1922- 1997)



The oil industry in the early 70s, assumptions:

1. Oil would remain plentiful;
2. Prices would remain low.

But: What if an accident in Saudi Arabia led to the severing of an oil pipeline? What would happen to global supply and prices?

1973 – Yom Kippur war / oil embargo:

1979 – Iranian Revolution

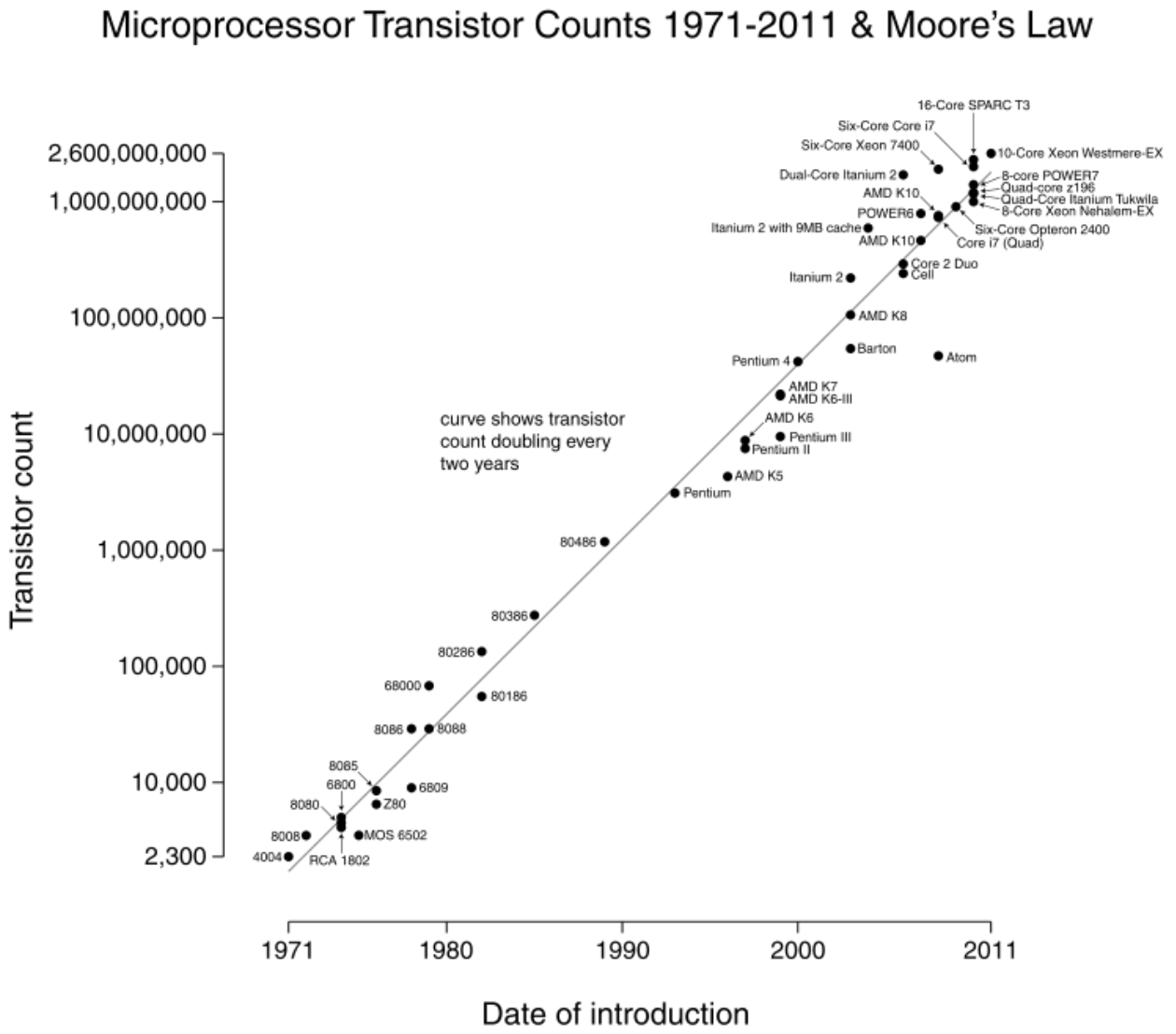
1980-1988 – Iran/Iraq war

1990 – Iraq invades Kuwait

And so on…

We are **not** accustomed to think in exponential terms, but some developments are exactly like that...

Eroom's Law in pharmaceutical R&D. The number of new drugs approved by the FDA per billion US dollars (inflation-adjusted) spent on R&D has halved roughly every 9 years. Scannell et al., 2012



the number of transistors on integrated circuits **doubles approximately every two years**

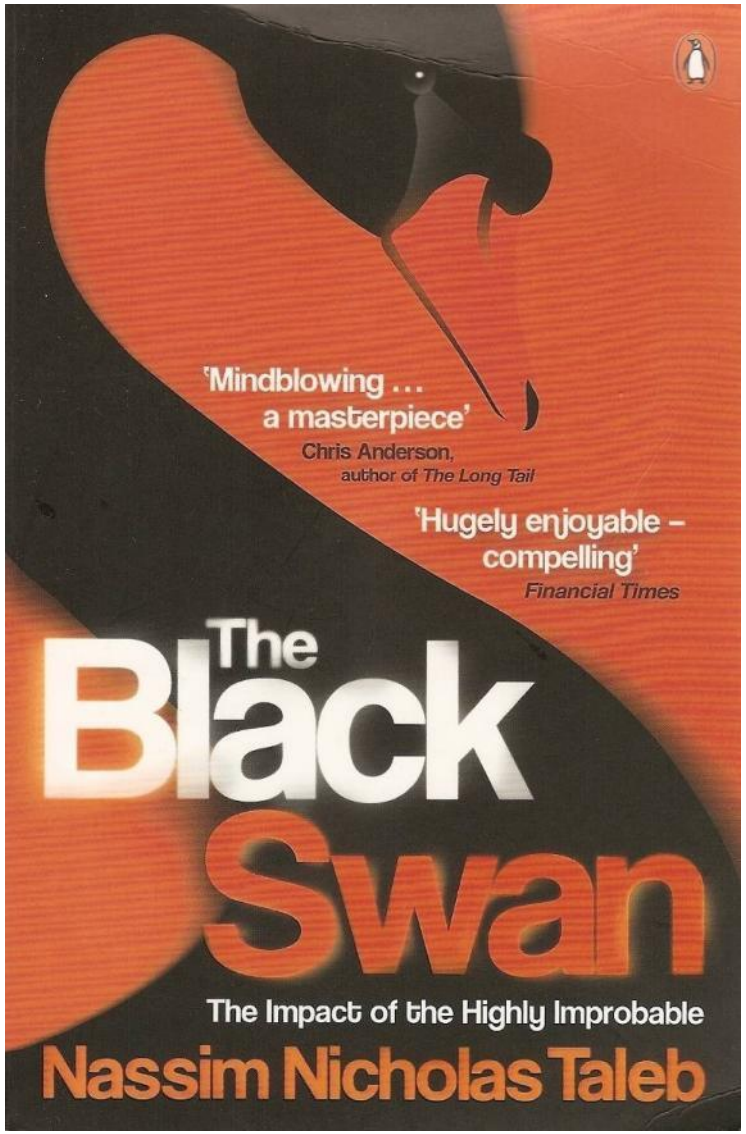
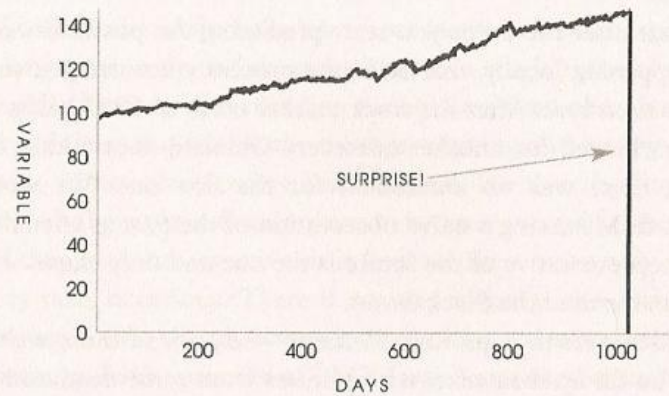


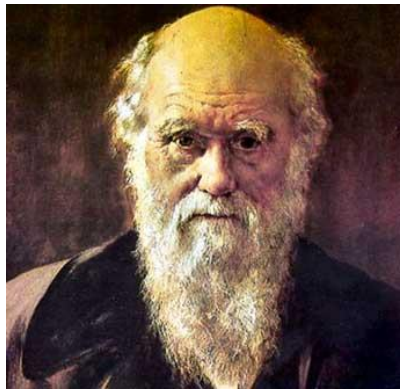
FIGURE 1: ONE THOUSAND AND ONE DAYS OF HISTORY



A turkey before and after Thanksgiving. The history of a process over a thousand days tells you nothing about what is to happen next. This naïve projection of the future from the past can be applied to anything.

Scenario analysis

- Scenario planning is about changing minds, not making plans
- Scenarios are not forecasts
- Scenarios are learning devices to take a long view and to open mental maps
- Think the unthinkable



Charles Darwin
(1809 - 1882)

And keep in mind:

It is ***not*** the survival of the fittest.....

It is the survival of those who can ***adapt best***

The world (of pharmaceutical sciences) out there is in a constant change anno 2009

- Rethinking the drug discovery and development process
- Therapeutic gaps are at the menu chart
- Rethinking the regulatory system
- Safety first/precautionary principle
- Payers in the hot seat
- Biologicals are changing the landscape
- Patient demand and societal mistrust
- Emerging countries
- Recessions, financial crisis

About 30 experts, including: investors, industry professionals, academics, regulators, NGOs

Time for an update????

What is the most important driver for the future?

1. Molecular biology, biomarkers, genomics
2. Information and other new (material) technologies
3. Rethinking pharma business model
4. Funding and investing models, risk sharing
5. Regulatory constraints and opportunities
6. Health care environment, payers in the hot seat
7. Therapeutic gaps, unequal access
8. Patient/public advocacy, zero risk culture, ethics
9. Demographics, longevity, chronic diseases
10. Globalization, emerging markets (BRIC countries)
11. Financial system

Update……. Add drivers
What is your number 1, 2 and 3?

Based on expert input we created 2 axes for scenario drivers

Attitude towards treatment and prevention of diseases

- Non-pharmacological

vs

- Pharmacological

Science Culture

- Dominance of entrepreneurial science

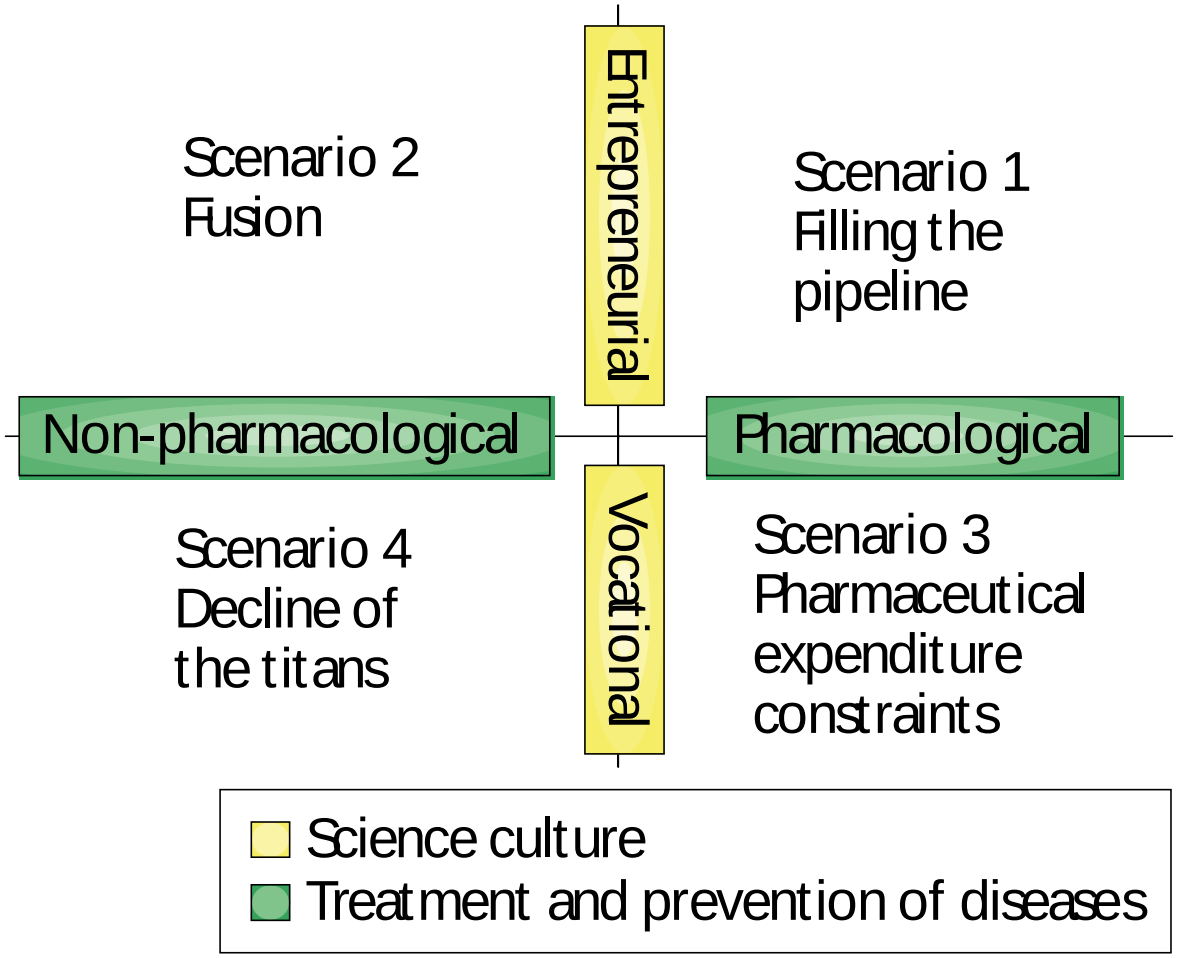
vs

- Dominance of vocational science

The 2 x 2 scenario matrix is the basis for the 4 scenarios narratives

- Decline of traditional pharma companies;
- Focus on devices and lifestyle technologies;
- New types of businesses emerge at interfaces.

- **Big pharma has disappeared. Focus of big companies on confirmatory trials/ production/ marketing;**
- **Drug development in SMEs and public institutes.**



- **The patent cliff has been crossed: big pharma dominant in innovation, SMEs as suppliers of early-stage developments;**
- **Governments are partners through PPPs.**

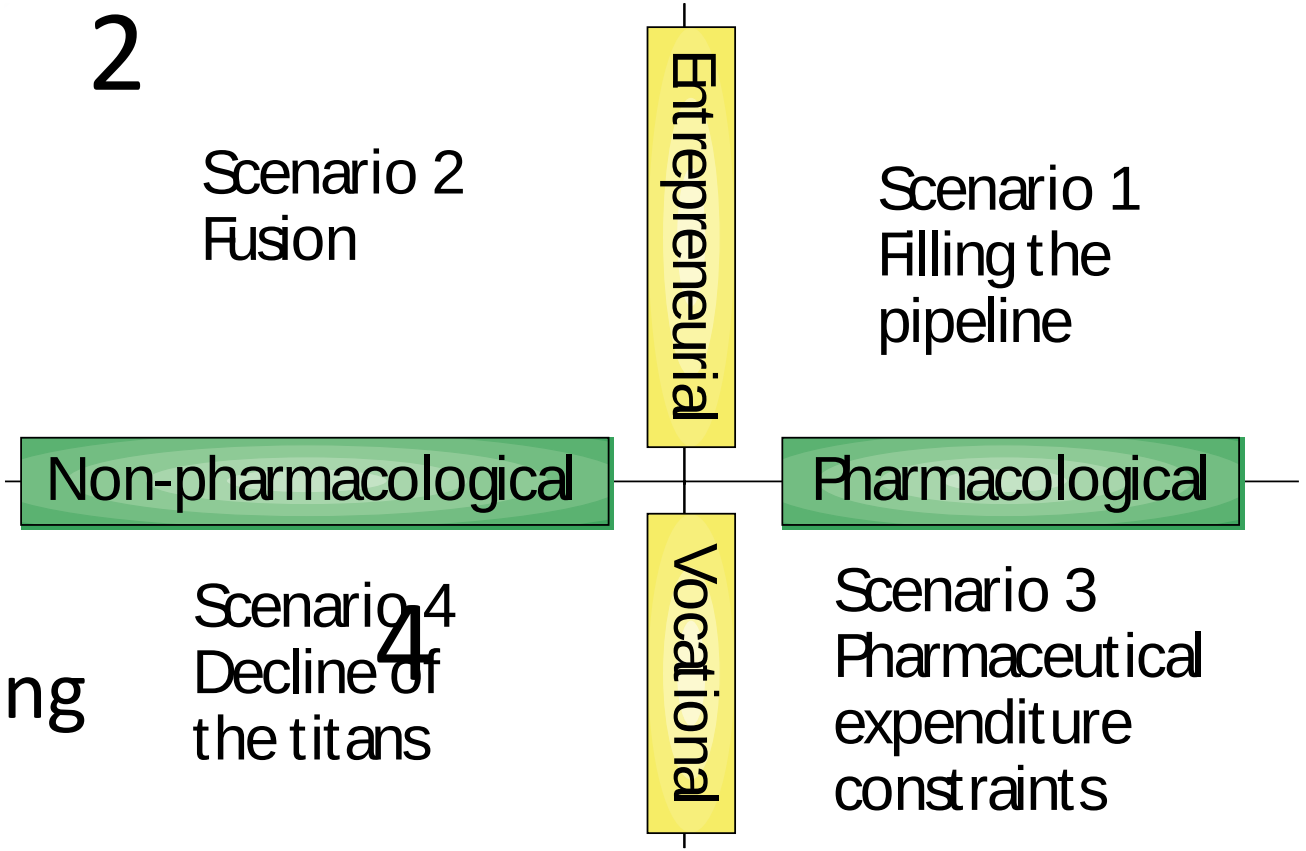
- **Separation of professions/industry vs academia**
- **Companies focus on niche markets in which added value can be shown best**
- **There is strong pressure to contain drug prices in major markets.**

Which scenario do you prefer?

Zauberflöte

2

Le nozze di Figaro

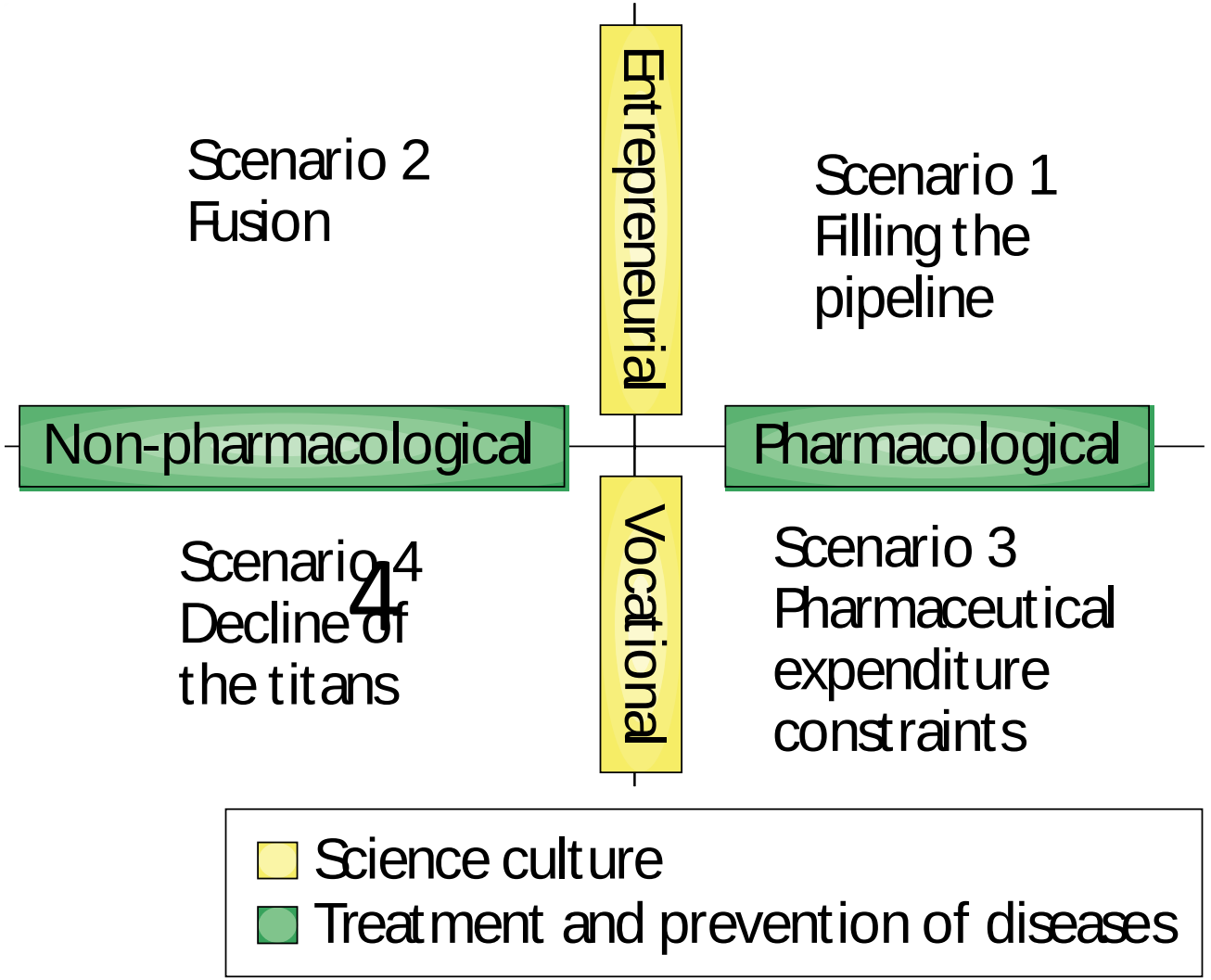


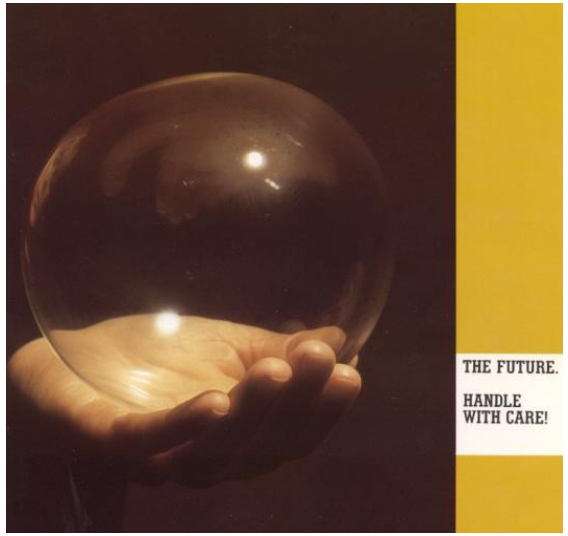
Gotterdämmerung

4

Faust

Which scenario do you think is most likely?





One of the fundamental tenets of scenario analysis is that it is probably better to **conduct** a scenario analysis than to **read/hear** about it!

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Commentary

The pharmaceutical sciences in 2020—Report of a conference organized by the Board of Pharmaceutical Sciences of the International Pharmaceutical Federation (FIP)

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FROM THE ANALYST'S COUCH

Pharmaceutical sciences in 2020

Daan Crommelin, Pieter Stolk, Luc Besançon, Vinod Shah, Kamal Midha and Hubert Leufkens

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Quick, quick, I must hurry.
There go the people. I must follow them
as I am their leader

Alexandre Ledru-Rollin, France 1807- 1864

(thanks to Mike Powell, Sofinnova)