Exploring the future of pharmacotherapy

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Declaration of interests

- Professor of Pharmacoepidemiology, Utrecht Institute of Pharmaceutical Sciences, 0.4 FTE.
- Chairman of the Dutch Medicines Evaluation Board (MEB), since mid 2007.
- Co-opted member of EMA PhVWP, 2006-2009; 2009-2015 co-opted member of EMA CHMP.
- Scientific Director WHO-Utrecht Collaborating Centre for Pharmaceutical Policy and Regulation, since 2008.
- This talk reflects my personal views; I am being inspired and challenged on a daily basis by many colleagues from these 'environments'.

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Edvard Munch: The dance of life, 1900

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Gustav Klimt: Death and Life, 2010

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A lot of future thinking, personal view …….

- Over the **last 15 years**, pharmacotherapy has made fascinating progress in terms of better products, diagnostics, in-process controls, better PK/PD, more data on effectiveness and safety, factoring in pharmacogenomics or HTA,
- but we still discuss the dosing of TNF blockers, safety of anticoagulants, use of antipsychotics in the elderly, strategies to beat AMR and many other therapeutic gaps, etc.
- Over the **next 15 years** the field will continue to blossom, both in science and clinical impact, but the future will be shaped primarily by socio-economic change and global health developments and challenges,
- rather than better molecules, biomarkers, roboting in supply chain management, e-health, or biosimilars, etc.

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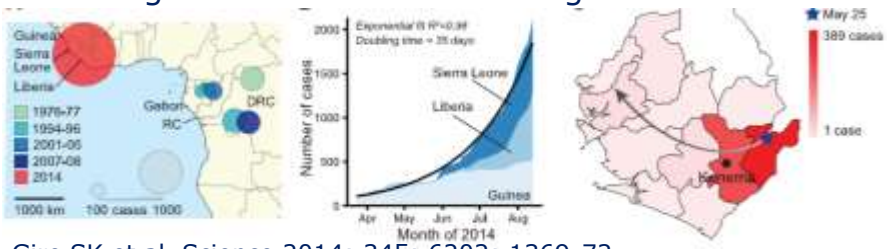
From 'blur' to learning about futures ……..

- With all this emerging science, transformative products will enter the clinic very soon …….
- This cancer drug shows promise, but at a price that many can't pay ……
- We'll see more biomarker/personalized therapies …..
- I am sitting here day after day at the EMA talking about future medicines my patients will never get access to …..
- Game changing advances in science represent just 10 percent of the key trends impacting health futures ……..
- Biosimilars have the future, we need to convince doctors …
- As a payer I only want to spend money on products that have shown clear OS benefit, I don't care about PFS …… …

Early spread of HIV-1 in human populations

Faria NR et al. Science 2014; 346: 56-61.

Ebola origin and transmisson during 2014 outbreak



Gire SK et al. Science 2014; 345; 6202: 1369-72.

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Exposure to HIV/Ebola	Exposure to medicines
Time/space	Time/space
Viral biology/evolution	Pharmacology of drug
Susceptibility factors	Patient characteristics
Social change	Indication
Economics	Prescribing/adherence
Transport/mobility	Health care/regulatory
Political/religious	Pharmaceutical market

⇨ Pharmacotherapy as a 'social construct'

Scenario analysis of the future of medicines

Hubert Leufkens, Flora Haaijer-Ruskamp, Albert Bakker, Graham Dukes

Planning future policy for medicines poses difficult problems. The main players in the drug business have their own views as to how the world around them functions and how the future of medicines should be shaped. In this paper we show how a scenario analysis can provide a powerful teaching device to readjust peoples' preconceptions. Scenarios are plausible, not probable or preferable, portraits of alternative futures. A series of four of alternative scenarios were constructed: "sobriety in sufficiency," "risk avoidance," "technology on demand," and "free market unfettered." Each scenario was drawn as a narrative, documented quantitatively wherever possible, that described the world as it might be if particular trends were to dominate development. The medical community and health policy makers may use scenarios to take a long term view in order to be prepared adequately for the future.

BMJ 1994; 309: 137-40.

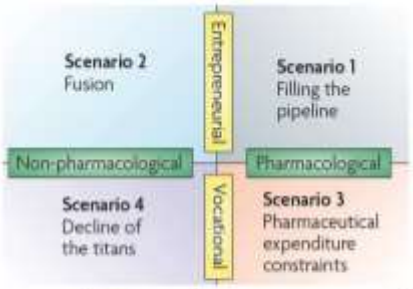

Figure 1 | **A matrix of four scenarios for the pharmaceutical sciences in 2020.**

Crommelin D, Stolk P, Besancon L, Shah V, Midha K, Leufkens H. Pharmaceutical sciences in 2020. Nat Drug Discov 2010; 9: 99-100.

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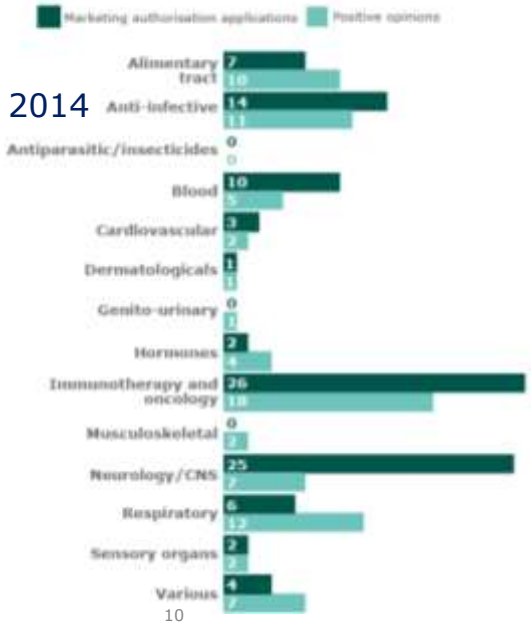
EMA Annual Report 2014



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Product discussions	Learning dimensions
ERT products rare diseases	B/R, dose/duration of therapy, registry building
ATMPs (cel, gene)	Quality, pharmaceutical formulation, GMP
Repositioning 'old' molecules (alfa-2 agonist, antioxidant, anticholinergic)	Quality, pharmaceutical formulation, clinical data
Biosimilar	Similarity exercise > quality, preclinical, clinical
Inhibitors of HDAC, Hh, MEK, BRAF, VEGF, proteasome	System biology, epi-genetics, biomarkers, B/R
Liposome formulation of antibiotic	Pharmaceutical formulation, GMP

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Product discussions	Learning dimensions
Extension to pediatric use (HIV, immune modulating products, insulins)	PK/PD, posology, pharmaceutical formulation
MABs (IL17, VEGF, HER2, CD30+, PD1)	System biology, immuno-logy, biotechnology, B/R
Vaccins, blood factors	Pharmaceutical formula-tion, immunology, B/R
Targeted therapy based on CFTR, exon skipping	Cell/system biology, protein science, genomics
NOACs, SGLT2 inhibitors, obesity products	B/R, safety monitoring, long-term CV outcomes
MS products	B/R, PML risk

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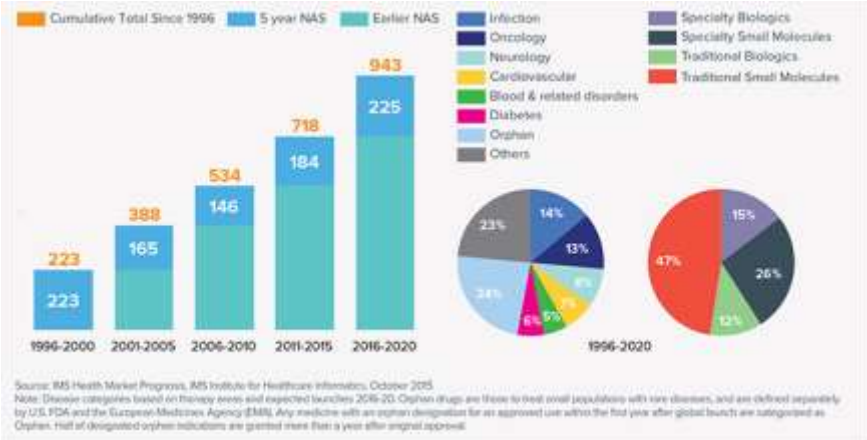
Outlook for 2020 ……..



Leufkens 2016 13

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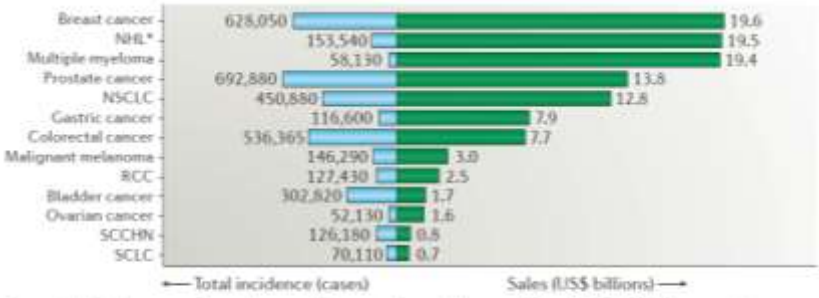

Figure 1 | **Incidence and major market oncology sales predicted for 2024.** Key oncology markets are expected to grow to over US$110 billion by 2024 across the seven major pharmaceutical markets (United States, France, Germany, Italy, Spain, United Kingdom and Japan). NHL, non-Hodgkin lymphoma; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; SCLC, small-cell lung cancer. Source: company reports. *NHL includes chronic lymphocytic leukaemia and small lymphocytic lymphoma.

Webster RM. Nat Rev Drug Discov 2016; 15: 81-82.

Leufkens 2016 14

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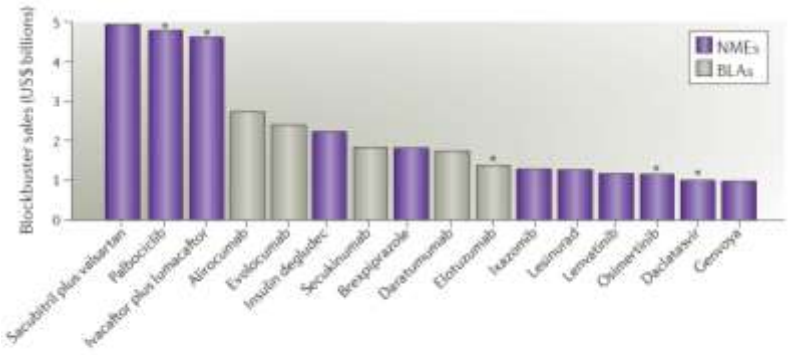

Figure 3 | **Anticipated blockbusters approved in 2015.** Sales forecasts are average, annual, global consensus sales estimates for 2020 as reported by Thomson Reuters' Cortellis database on 31 December 2015. BLA, Biologics Licence Application; NME, new molecular entity. *Drugs with breakthrough designation.

Mullard A. Nat Rev Drug Discov 2016; 15: 74-76.

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Key drivers for the future ….

- Non-data space (regulatory, HTA, clinical) becomes more critical.
- Increasing variance in access to medicines across Europe.
- Response to global needs and challenges.

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Key questions in the lifecycle of a medicine

Question	Today's challenges
Robust definition and diagnosis of disease?	Psychiatric morbidities, sepsis, somatic functional disorders
Clinically relevant endpoints to evaluate drug effects?	6-MWT in PAH, HbA1C in diabetes, PFS/OS in cancer
Identifiable target population (indication) that may benefit?	Biomarkers to identify responders and non-responders
What kind of comparison is useful, needed and feasible?	Placebo, active controls and dynamics in treatment options

FROM THE ANALYST'S COLL

Factors influencin
of new drugs in Eu

Michelle Putzeist, Aukje K. Mantel-Tee
Malcolm Rowland, Christine C. Gispe
Arno W. Hoes, Hubert G. M. Leufkens and Hans-Georg Eichler

Possible Type I error: 42 products showed a confirmatory phase with pertinent uncertainties; still 24/42 were approved.

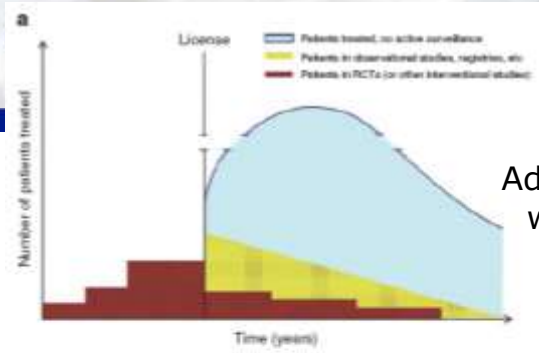
Possible Type II regulatory error: 26 products showed a convincingly positive confirmatory phase; still 5/26 were not approved.

Table 3 | **Summary table of EMA assessment* of development plan‡**

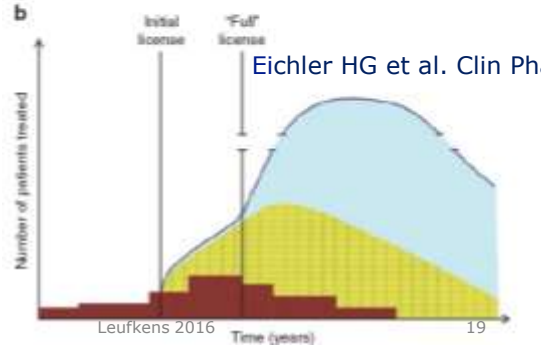
Development plan		Non-approved (n = 23)	Approved (n = 45)	Relative risk of non-approval (95% CI)
Learning phase	Confirmatory phase			
+	+	2 (11%)	16 (89%)	Reference
+	–	5 (25%)	15 (75%)	2.3 (0.4–11.6)
–	+	3 (37%)	5 (63%)	3.4 (0.6–20.2)
–	–	13 (59%)	9 (41%)	5.3 (1.2–23.6)

CI, confidence interval; EMA, European Medicines Agency. *Definitions of positive (+) and negative (–) scores are given in Supplementary information S2 (box). ‡Categorized for learning and confirmatory phase. A positive score in both phases was taken as the reference.

Nat Rev Drug Discov 2012; 11: 903-4.



Adaptive licensing opens a window for observational studies, registries and pragmatic trials



Eichler HG et al. Clin Pharmacol Ther 2012; 91: 426-37.

CBG MEB

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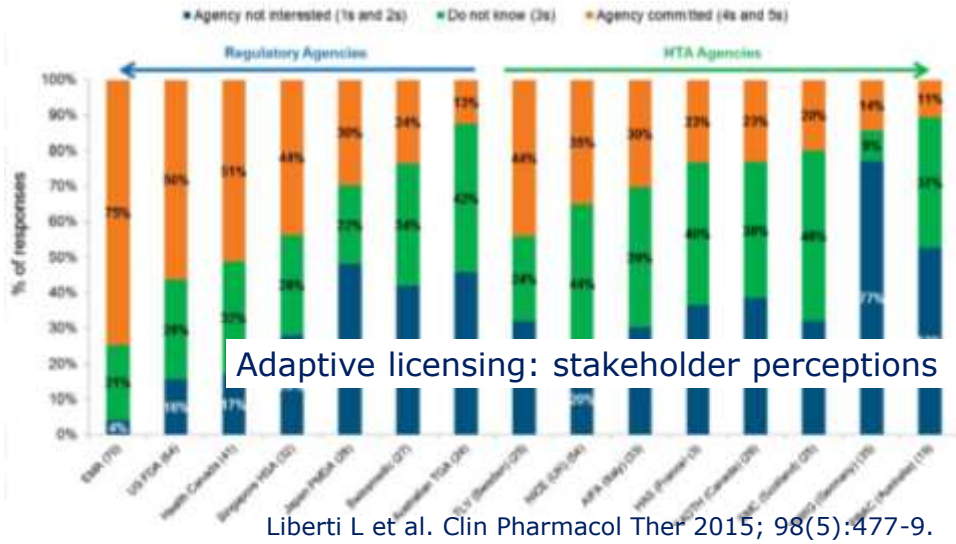

Adaptive licensing: stakeholder perceptions

Liberti L et al. Clin Pharmacol Ther 2015; 98(5):477-9.

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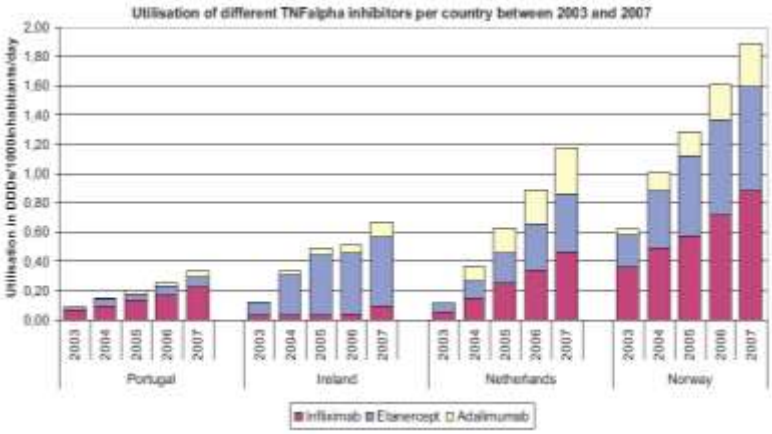
Variability use TNF alpha blockers



Hoebert JM et al. Health Policy 2012 Jan;104(1):76-83.

Cancer drugs in 16 European countries, Australia, and New Zealand: a cross-country price comparison study

Lancet Oncol 2016; 17: 39–47.

Summary

Background Cancer drugs challenge health-care systems because of their high prices. No cross-country price comparison of cancer drugs for a large number of countries has been published. We aimed to survey the prices of cancer drugs in high-income countries (Europe, Australia, and New Zealand).

Methods Based on comparability in terms of the economic situation and of the pharmaceutical system, we surveyed official list prices per unit at ex-factory price level of 31 originator cancer drugs in 16 European countries, Australia, and New Zealand as of June, 2013. Drug price data for the European countries were provided by the Pharma Price Information (PPI) service; Australian and New Zealand drug price data were retrieved from the respective pharmaceutical schedules.

Findings In Austria, Denmark, Finland, Germany, Ital for all or all but one drug surveyed whereas the availabi especially in New Zealand and Portugal. The differe lowest priced country varied between 28% and 388%. and upper outliers (particularly prices in Switzerland level, whereas Sweden, Switzerland, and Germany sh

Harten W et al. Lancet Oncol 2016; 17: 18–20.

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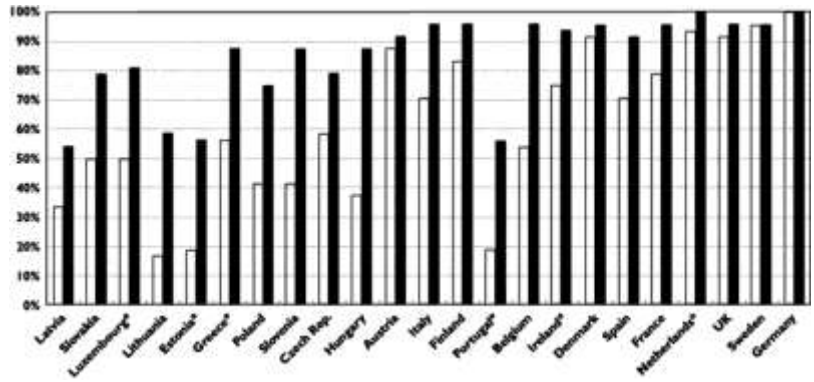
Uptake of new medicines in Europe: availability of 2004 approvals



Hoebert JM, Irs A, Mantel-Teeuwisse AK, Leufkens HG. Br J Clin Pharmacol 2013; 76:1-6.

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Policy measures and economic stability, EU 2008-2011

	Economically stable countries*			Economically less stable countries*				
	Austria	Estonia	Finland	Greece	Ireland	Portugal	Slovakia	Spain
Pricing								
Price cuts	0	0	0	2	2	3	0	4
External price referencing	0	0	0	3	0	2	2	1
Distribution remuneration	0	1	0	3	3	3	0	3
VAT on medicines	1	1	0	1	1	1	0	1
Extraordinary price review	0	0	0	2	2	1	1	1
Reimbursement								
Internal reference pricing	0	1	1	1	0	2	2	1
Out-of-pocket payments	4	1	0	0	1	5	3	2
Delisting	0	0	1	2	0	1	0	1
Generics								
INN prescribing	0	1	0	0	0	1	1	1
Generic substitution	0	0	0	0	0	0	0	0
Public campaigns and other generic policies	1	2	0	0	1	3	1	2
Total	6	7	2	14	10	22	10	17

Leopold C et al. Effect of the economic recession on pharmaceutical policy and medicine sales in eight European countries. WHO Bull 2014; 92(9):630-640.

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How to navigate to a sustainable future of medicines in a global context?

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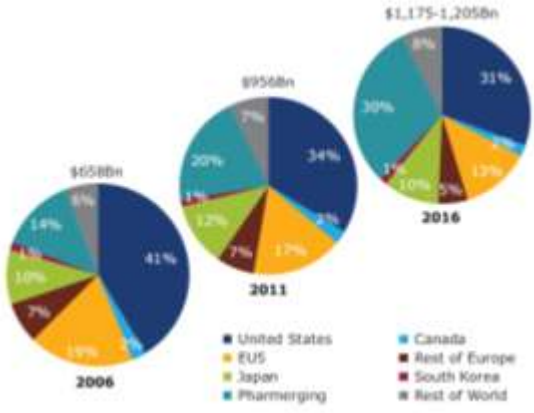
Spending on medicines per geographic region



IMS Institute for Healthcare Informatics. The Global Use of Medicines: Outlook Through 2016, 2012.

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Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union

JAMA 2008; 300: 1887-1896.

Thijs J. Giezen, PharmD
Sabine M. J. M. Straus, MD, PhD
Ruud Scholtkens, PhD
Robert G. M. Leufkens, PhD
Antoine C. G. Egberts, PhD

Context Biologicals are a relatively new class of medicines that carry specific risks

JOURNAL OF CLINICAL ONCOLOGY REVIEW ARTICLE

2011 Jun 1;29(16):2266-72.

Evaluation of Oncology Drugs at the European Medicines Agency and US Food and Drug Administration: When Differences Have an Impact on Clinical Practice

Francesco Trotta, Robert G.M. Leufkens, Jan H.M. Schellens, Richard Laing, and Giovanni Tafuri

ABSTRACT

Purpose
The aims of this study were to compare the approaches of the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in the evaluation and approval of new anticancer indications and to identify possible clinical implications associated with these differences.

Methods
Information on the European Union therapeutic indications for the cohort of anticancer drugs was extracted from the European Public Assessment Reports and from the FDA review reports.

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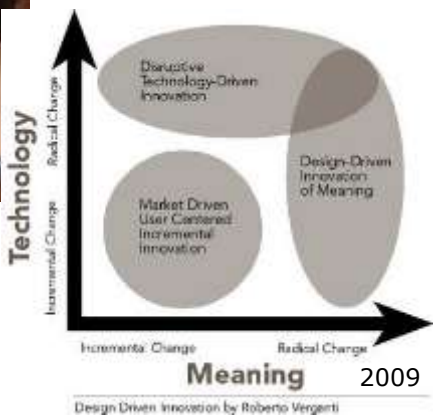
There is more than one approach in medicine …..

Design-driven innovations need 'interpreters', i.e. actors who listen, connect, translate, give meaning to things (MEDICINES) and come with innovative, meaningful proposals.



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The future of pharmacotherapy?

- The fundamentals will probably not change dramatically, further sophistication, technology platforms.
- Much better taxonomy of the 'critical uncertainties' (both efficacy/effectiveness and safety) of modern medicines.
- Increasing awareness and understanding that pharmacotherapy is a 'social construct'; diversification of the culture of medicines' use.

Strong future of 'integrative' pharmacotherapy: the hospital pharmacist as interpreter.