DRUG REPURPOSING - industry perspective

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2008 products – classic blockbuster, high prevalence

TOP 10 PRODUCTS

For the 12 months ending June 2008, Lipitor retains its spot as the world's biggest-selling drug

	COMPOUND	MARKETER	INDICATION	SALES TO JUNE 2008 ($ BILLIONS)	12-MONTH CHANGE IN SALES
Lipitor	Atorvastatin	Pfizer	Hypercholesterolemia	$13.8	-2.1%
Plavix	Clopidogrel	Bristol-Myers Squibb	Atherosclerotic events	8.3	33.4
Nexium	Esomeprazole	AstraZeneca	Acid reflux disease symptoms	7.7	7.5
Serentide	Fluticasone and salmeterol	GlaxoSmithKline	Asthma	7.5	7.4
Enbrel	Etanercept	Amgen	Rheumatoid arthritis	5.6	11.9
Seroquel	Quetiapine	AstraZeneca	Bipolar disorder, schizophrenia	5.1	17.9
Zyprexa	Olanzapine	Eli Lilly & Co.	Schizophrenia	5.1	-1.2
Risperdal	Risperidone	Johnson & Johnson	Schizophrenia	5.0	0.8
Remicade	Infliximab	Centocor	Crohn's disease, rheumatoid arthritis	4.7	15.7
Singulair	Montelukast	Merck & Co.	Asthma, allergies	4.6	8.7
Top 10 products				$67.4	8.3%

NOTE: Sales are in U.S. dollars for the 12 months ending June 2008. **SOURCES:** IMS Health, MIDAS

hypercholesterolemia… 13%
atherosclerotic event……6%
reflux disease……20-40%
asthma……7-8%

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2018 products – even bigger in sales, small prevalence, nearly all biologicals

Company	Names	Sales
AbbVie	Humira (Adalimumab)	21 billion
Celgene	Revlimid (Lenalidomide)	9.2 billion
Amgen/Pfizer	Enbrel (Etanercept)	7.3 billion
Regeneron/Bayer	Eylea (Aflibercept)	6.5 billion
Roche	Avastin (Bevacizumab)	6.4 billion
Roche	Herceptin (Trastuzuma)	6.4 billion
Roche	Rituxan (Rituximab)	6.4 billion
Jonhson& Johnson	Remicade (Infliximab)	6.3 billion
Jonhson& Johnson/Bayer	Xarelto (Rivaroxaban)	6.1 billion
Merck	Keytruda (Pembrolizumab)	6.1 billion

Rheumatoid arthritis…….0,5-1,0% (prevalence)
Multiple myeloma……..5/100 000 (incidence)
Macular degeneration...0,7% (50-60 years)
Lung cancer……62/100k (incidence)

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Value Added Medicines categories

reformulation - better dosage forms or strength for specific patient group

combinations - more drug substances, but also medicines with novel devises or services

repositioning – discovery of novel uses and indications for known compounds

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Reference: Generics bulletin , 20 Oct 2017

New modified release product

superiority to placebo

superiority to placebo and non-inferiory to IR product

647 subjects in 2RCT of gabapentin enacarbil development, ~100 per study arm

~200 patients per study arm

price: $414 per box of 30 tbl.

same price like for IR product*

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* Carbamazepin IR + SR example
SR forms of pramipexol, phenytoin, lamotrigin, topiramete, levetiracetam, gabapentin only in US

Innovative fixed dose combinations

compliance known to improve outcomes (Jung 2013)

several FDC products registered based on BE comparison to individual components + interaction, prescription data and summary of literature

little or no premium

2017 – updated FDC guideline

Randomised controlled trials (RCT) to prove superiority in insufficient responders to the one (or more) active substances of the fixed combination medicinal product are required to demonstrate that the fixed combination medicinal product has greater efficacy in comparison with the respective individual active substances. Superiority or 'add on efficacy' can only be claimed to active substances to which patients have been demonstrated to be responding insufficiently. The usual approach is that patients

still no premium

in contrast to therapeutic guidelines: use FDC as initial therapy

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Management of hypertension: start with SPC*

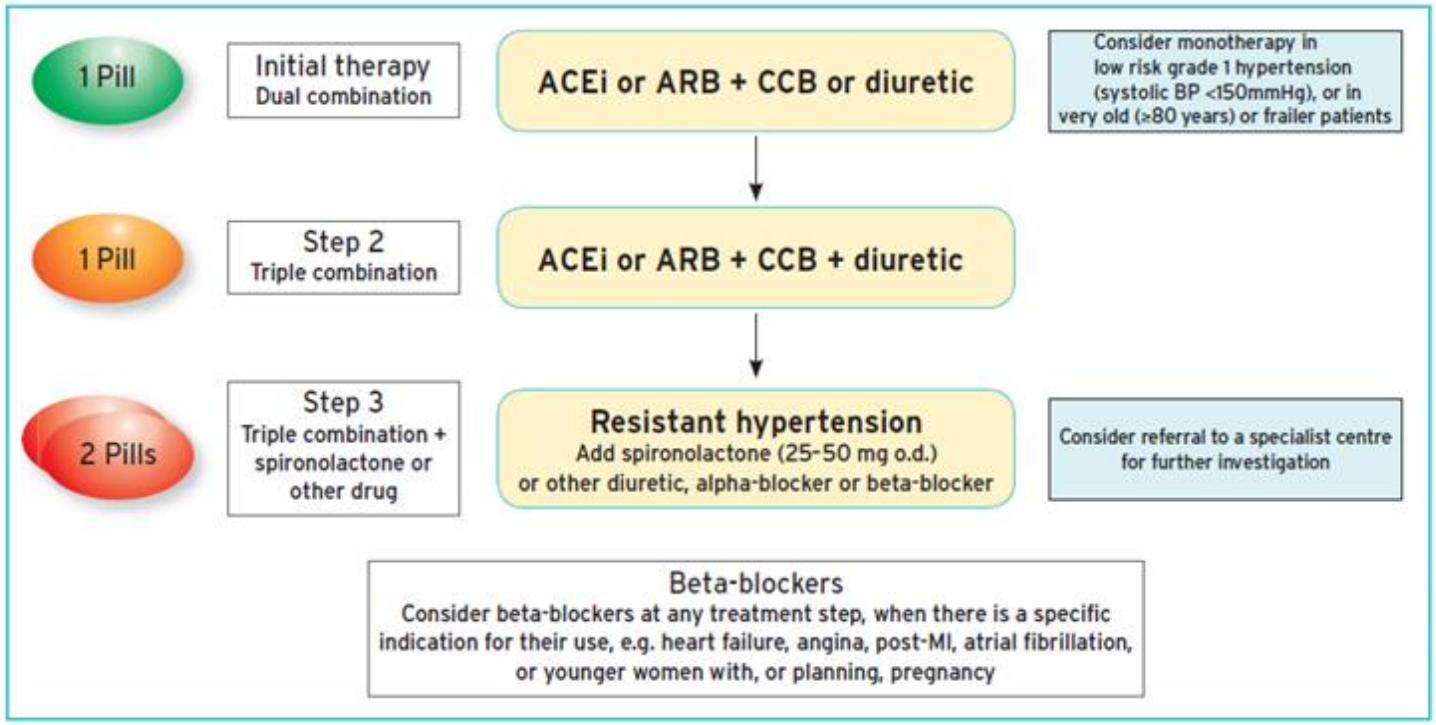

Figure 4 Core drug treatment strategy for uncomplicated hypertension. The core algorithm is also appropriate for most patients with HMOD, cerebrovascular disease, diabetes, or PAD. ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; HMOD = hypertension-mediated organ damage; MI = myocardial infarction; o.d. = omni die (every day); PAD = peripheral

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Reference: 2018 ESC/ESH Guidelines for the management of arterial hypertension
*SPC – single pill combination

Antiasthmatic devices

known components, innovative device with intuitive handling, moisture protection, orientation independence

Regulatory pathway in EU:
prove of bioequivalence

Development reality:
6 PK studies supplemented by
3 PD studies (BE not possible to be achieved)

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Reference: GUIDELINE ON THE REQUIREMENTS FOR CLINICAL DOCUMENTATION FOR ORALLY INHALED PRODUCTS (OIP) INCLUDING THE REQUIREMENTS FOR DEMONSTRATION OF THERAPEUTIC EQUIVALENCE BETWEEN TWO INHALED PRODUCTS FOR USE IN THE TREATMENT OF ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) IN ADULTS AND FOR USE IN THE TREATMENT OF ASTHMA IN CHILDREN AND ADOLESCENTS, EMA, 2009

Repurposing is the process by which an object with one use value is transformed or redeployed as an object with an alternative use value.

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Drug repositioning

drug repositioning (drug repurposing, re-profiling, re-tasking or therapeutic switching) is the application of known drugs to treat a different disease

smaller companies (NovaLead Pharma,Ore Pharmaceuticals, Biovista, Numedicus, Melior Discovery , SOM Biotech) are performing drug repositioning on a systematic basis

(in silico biology and in vivo/in vitro experimentation to assess a compound and develop and confirm hypotheses concerning its usage for new indications)

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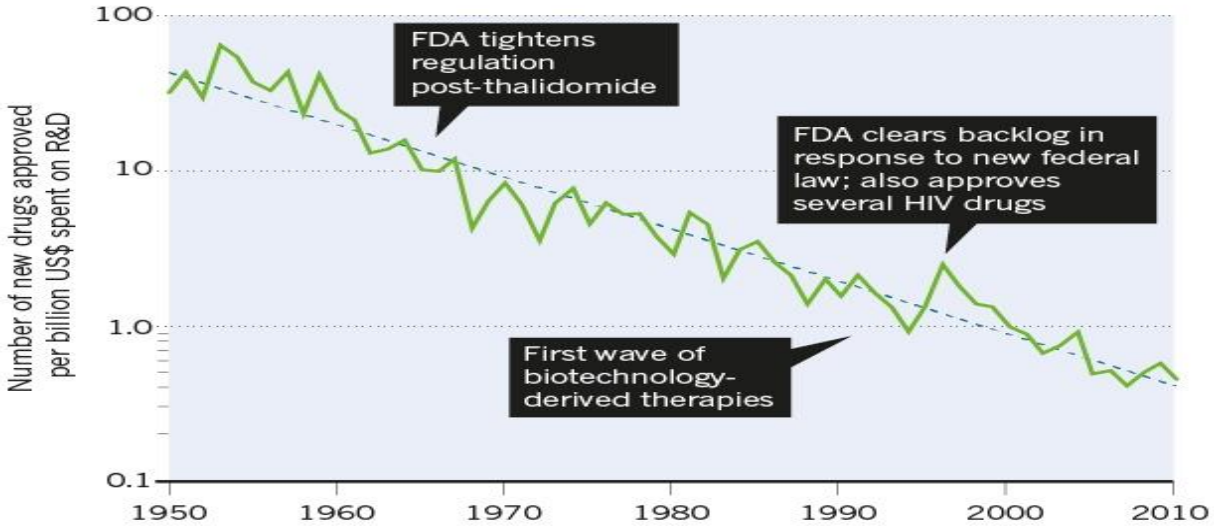
Generic drugs are the easiest target ?

EROOM'S LAW

The efficiency of research and development of new drugs in the United States halves every nine years or so. Drug developers sometimes call this Eroom's law — Moore's law for microprocessors in reverse. Repositioning drugs could help to counter this decline.



A SHORTER TIMESCALE

Because most repositioned drugs have already passed the early phases of development and clinical testing, they can potentially win approval in less than half the time and at one-quarter of the cost.

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Sources:
https://www.nature.com/news/can-you-teach-old-drugs-new-tricks-1.20091

New therapeutic opportunities for existing drugs

"Drug repurposing is a promising strategy in pharmaceutics, since it reduces considerably the resources needed for developing any given therapy for a disease and magnifies the probability that the drug enters from Phase I to market for the new indication" (Temesi et al., 2014).

Successful repurposing cases in the market	2017 value[(1)] in EU	Other cases
1 Dimethyl Fumarate (Tecfidera (dimethyl fumarate) delayed-release capsules) • Have been used for over 50 years to treat psoriasis. • Relaunched by Biogen in 2014 for the treatment of multiple sclerosis.	**€ 735M**	Minoxidil – Hypertension → Hair regrowth Ropinirole – Parkinson's → Restless leg synd.
2 Sildenafil (VIAGRA (sildenafil citrate) tablets) • Sildenafil, sold as Viagra since 2005, was tested as a treatment for erectile dysfunction only after erections emerged as a side effect in Phase 1 trials for cardiovascular disease.	**€ 402M** genericized	Buprenorphine – Pain → Opiod addiction
3 Thalidomide (THALOMID (thalidomide) Capsules 50 · 100 · 150 · 200 mg) • Originally approved in Europe in the 1950's as a sedative. • Relaunched in 2000's by Celgene for the treatment of multiple myeloma.	**€ 29M** genericized	Zivudine – Failed as chemo → HIV ASA – anti-inflammat. → Anti aggregant

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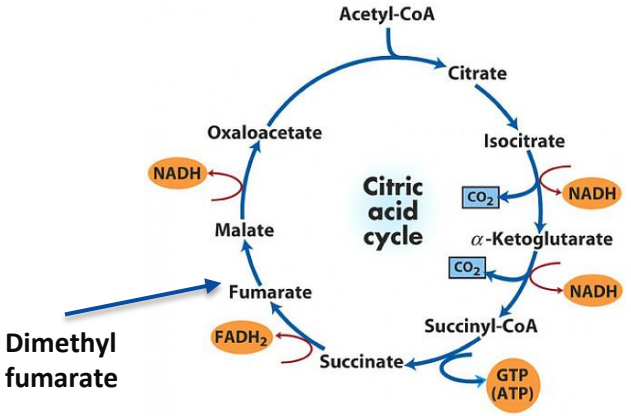
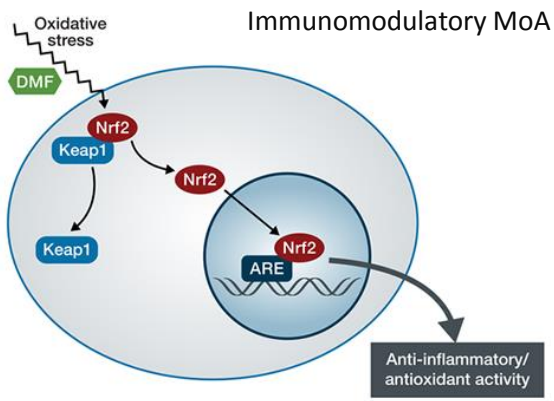
Sources:
https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/drug-repositioning
https://www.the-scientist.com/?articles.view/articleNo/47744/title/Repurposing-Existing-Drugs-for-New-Indications/
(1) IMS Q3.2017

Dimethyl fumarate repurposing

- from psoriasis to multiple sclerosis





MoA exploration

1958 **1994** **2013** **2017**

Magistral preparations
used for treatment of **psoriasis**

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Fumaderm®
registered in Germany

psoriasis

Tecfidera®
registered in US

multiple sclerosis

Clinical program extensiveness depends on indication

Multiple sclerosis (Tecfidera®)

DEFINE study (N=1237)

Tecfidera 240 mg BID (N=411)
Tecfidera 240 mg TID (N=416)
Placebo (N=410)

CONFIRM study (N=1430)

Tecfidera 240 mg BID (N=362)
Tecfidera 240 mg TID (N=345)
Glatiramer acetate 20 mg (N=360)
Placebo (N=363)

Outcome measures:

Annualized relapse rate
Disease progression
Freedom of disease
MRI (T2-, T1- and Gd-enhancing lesions)
96 weeks

130 mio €

Plaque psoriasis (Otezla®)

PSOR-008 study (N=825)

Apremilast 30 mg BID (N=550)
Placebo (N=405)

PSOR-009 study (N=405)

Apremilast 30 mg BID (N=270)
Placebo (N=135)

Outcome measures:

PASI (Psoriasis Area and Severity Index)
sPGA (Static Physicians Global Assessment)
Body Surface Area; Pruritus
VAS, Dermatology QoL Index
16 weeks

25 mio €

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Abraxane benchmark

IQVIA consulting for Medicines for Europe

Abraxis combined paclitaxel with albumin-binding technology to enhance delivery to the tumour cells

Molecule: Nab-Paclitaxel; **paclitaxel** is a hydrophobic mitotic inhibitor belonging to the group of taxanes which are potent cytotoxic diterpenes and the **Nab technology** enables targeted delivery of chemotherapeutics to the tumour

Value added medicine	
Manufacturer	Abraxis (Celgene from 2013)
Brand name	Abraxane
Indication	Approved in 3 tumours: 1. 2L metastatic breast cancer; 2. 1L pancreatic cancer (with gemcitabine); 3. 1L NSCLC (with carboplatin)
Form	Protein-bound particles for IV infusion
Dosage	Varies by indication
EMA approval	2008 Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Originator	
Manufacturer	BMS
Brand name	Taxol
Indication	Approved in 4 tumours: 1. Adjuvant node-positive breast cancer; 2L locally advanced or metastatic breast cancer (single agent or with an anthracycline or trastuzumab); 2. 1L NSCLC; 3. 1L (with cisplatin) /2L ovarian cancer; 4. Advanced AIDS-related Kaposi's sarcoma
Form	Suspension for IV infusion
Dosage	Varies by indication
Approval	1993 (first MIDAS sales)

An EU patent is active on the nab technology used for Abraxane delivery

NSCLC – non small cell lunch cancer

Source: IQVIA MIDAS, IQVIA HTA Accelerator, IQVIA internal expertise, EMA website; news-medical website

IQVIA_MfE_Case Studies for VAMs - Findings Presentation_May 2018

Abraxane benchmark: description of clinical added value

IQVIA consulting for Medicines for Europe

Abraxane originally launched in to breast cancer, extending overall survival and reducing administration time

Abraxane value proposition in Breast Cancer

Improved delivery mechanism reduces administration time

- Nab-driven chemotherapy provides a new paradigm for **penetrating the blood-stroma barrier to reach the tumour cell**
- **Treatment time shortened to 30-minutes**, without premedication, instead of 3 hours for Taxol

Increased overall survival in breast cancer

- **Increased overall survival** in second-line metastatic breast cancer patients
- **Doubled response rate**, presenting an 85% ORR* in patients who had failed combination therapy or relapsed within 6 months of adjuvant treatment

Alternative safety profile

- The Nab technology in enables a **solvent-free formulation which reduces incidence of toxicities**; while some side effects improve, others worsen:
  - (+) **Reduced neutropenia and hypersensitivity** reactions than originator
  - (-) Higher incidence of peripheral neuropathy, nausea, vomiting, diarrhea and asthenia

*ORR = Overall Response Rate

Source: IQVIA expertise; Celgene website; seeking alpha

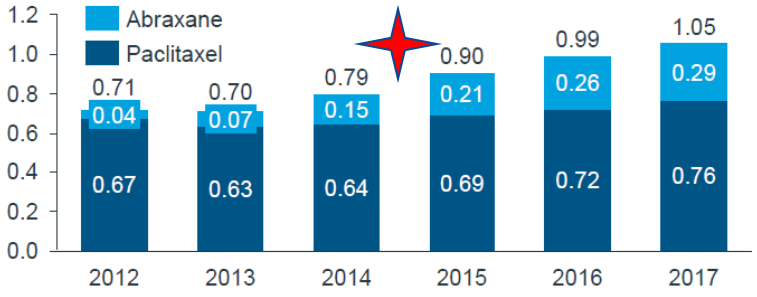
IQVIA_MfE_Case Studies for VAMs - Findings Presentation_May 2018

Abraxane benchmark: reflection of clinical benefits by payers

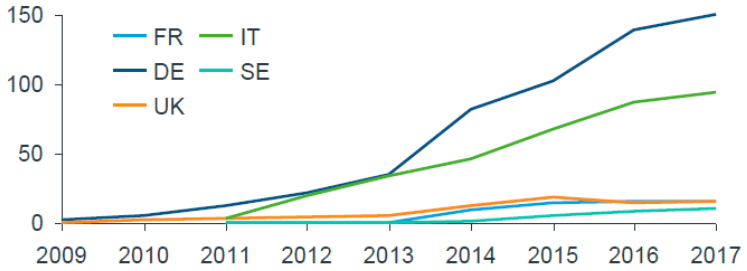
IQVIA consulting for Medicines for Europe

Since it's launch in 2008, Abraxane sales have grown strongly, largely as a result of further indication expansions

Abraxane annual market share of paclitaxel market by volume in M SU



Abraxane annual volume sales in '000 SU



Note: Abraxane is not available in PL

Source: IQVIA HTA Accelerator; IQVIA MIDAS; Press reader; *CDF = cancer drugs fund;

IQVIA_MfE_Case Studies for VAMs - Findings Presentation_May 2018

- Total paclitaxel/Abraxane market **grew by nearly 50% between 2012 and 2017**, led by Abraxane
  - **Indication expansions** into pancreatic cancer (2014) and NSCLC (2015) are key drivers of growth
    - In DE, SE and UK, there is a clear spike in 2014 following pancreatic indication expansion
    - Increase between 2015 and 2016 is evident but less significant, demonstrating some success in NSCLC
- In the UK, sales dipped from their peak in 2015 after Abraxane was **delisted from the CDF*** due to cost-effectiveness; this was subsequently overturned (2016) after price was lowered through a patient access scheme
- Abraxane had limited success in FR as it is not included on the *liste en sus* due to the combination of ASMR IV and its comparator (paclitaxel) not being on the list itself; this resulted in exclusion from some hospital formularies

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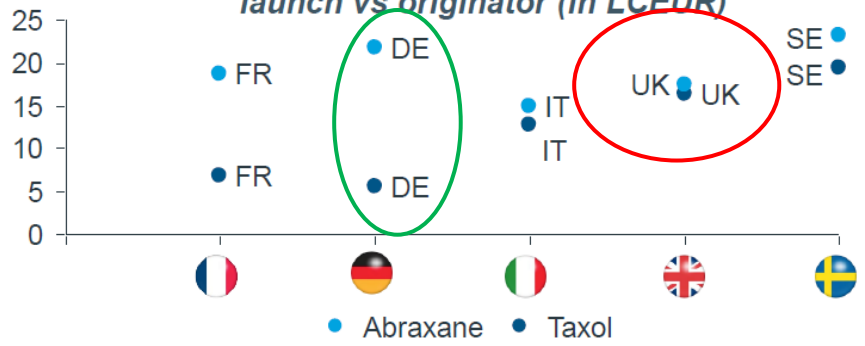
Abraxane benchmark: which is the most rewarding country in EU?

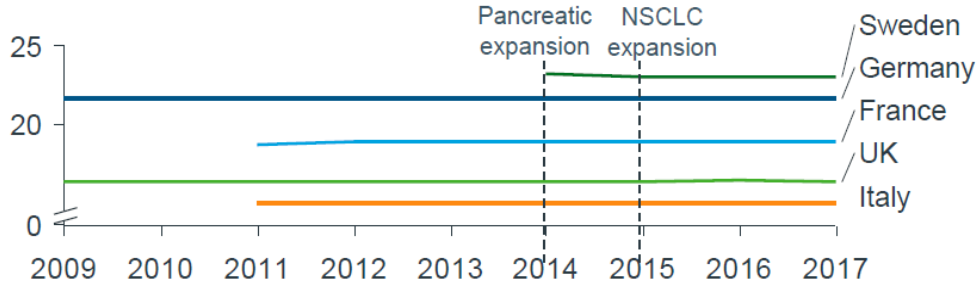
IQVIA consulting for Medicines for Europe

Abraxane achieved significant premiums over originator at launch; a higher price in SE is a result of approval only in pancreatic

Abraxane price per treatment course (18 mo, ex-MNF in '000) at launch vs originator (in LCEUR)



Abraxane treatment price (18 mo, ex-MNF, in '000) evolution (in LCEUR)



Note: Abraxane is not available in PL

- Abraxane achieved a **large price premium** vs. paclitaxel in Germany, where it did not have an HTA assessment and could price freely and in France where it achieved ASMR IV
- Price in SE, UK and IT was close to Taxol at launch and stayed constant throughout
  - However, Celgene offered a confidential discount via patient access schemes (PAS) in the UK in 2015 after Abraxane had been delisted from the CDF
- Abraxane is only approved for pancreatic cancer in Sweden, a more severe disease, possibly justifying a higher price
- Subsequent tumour expansions for Abraxane did not erode price in other EU6 countries

Source: IQVIA HTA Accelerator; IQVIA MIDAS; IQVIA expertise; cross checked with IQVIA pricing insights where available; *CDF = cancer drugs fund;

Before taking off

Added value in selected indication agreed with stakeholders

Evidence required

full preclinical and clinical program X flexibility on the design of studies

Reimbursement

internal reference pricing X most economically advantageous tender (MEAT)

(transparent system with defined pricing and criteria and metrics)

Non financial incentives like regulatory exclusivity period

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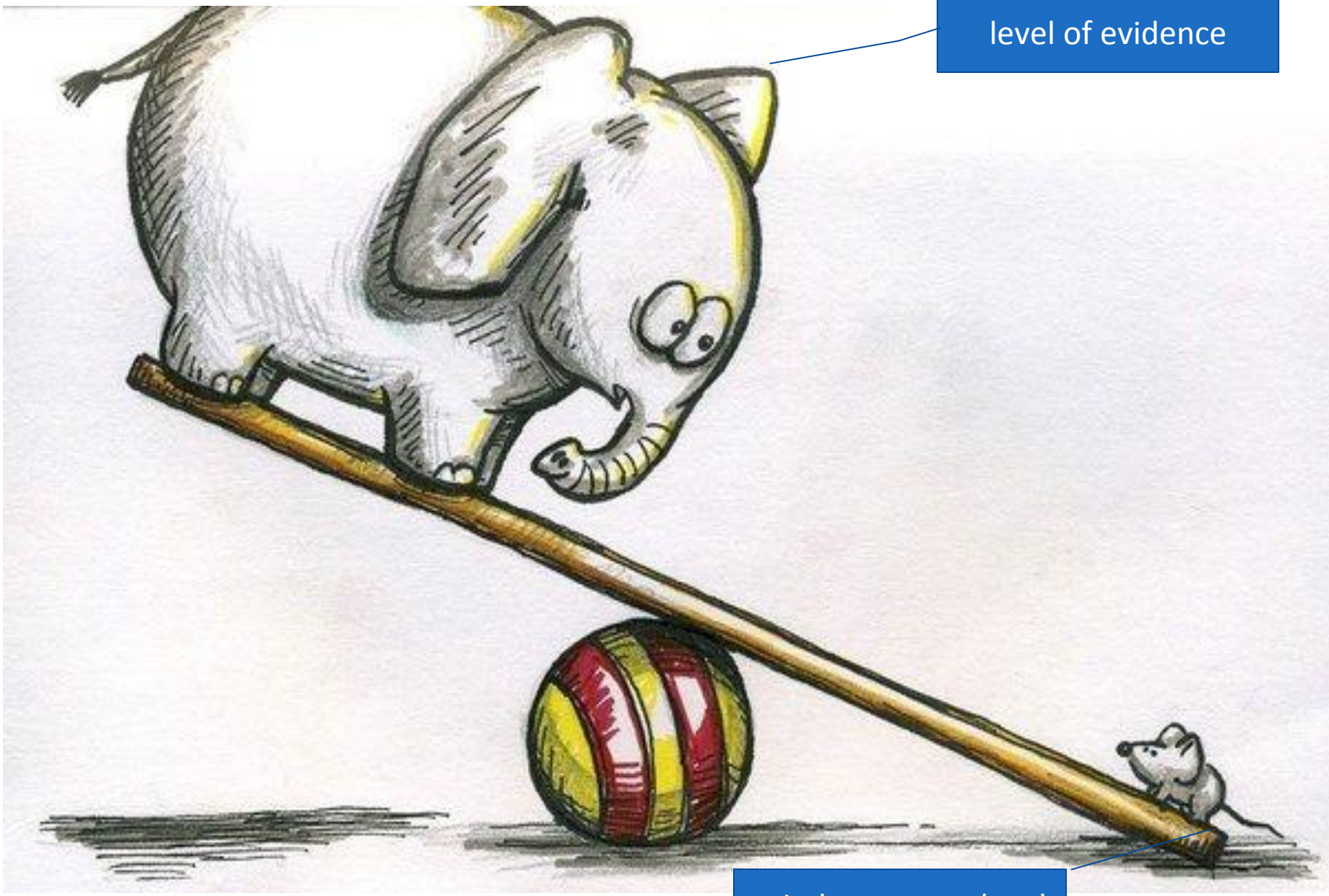

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