Overview of the new marketplace in 2017 and beyond

11th International Pharmaceutical and Medical Device Compliance Conference
Frank Wartenberg, President Central Europe

May 2017

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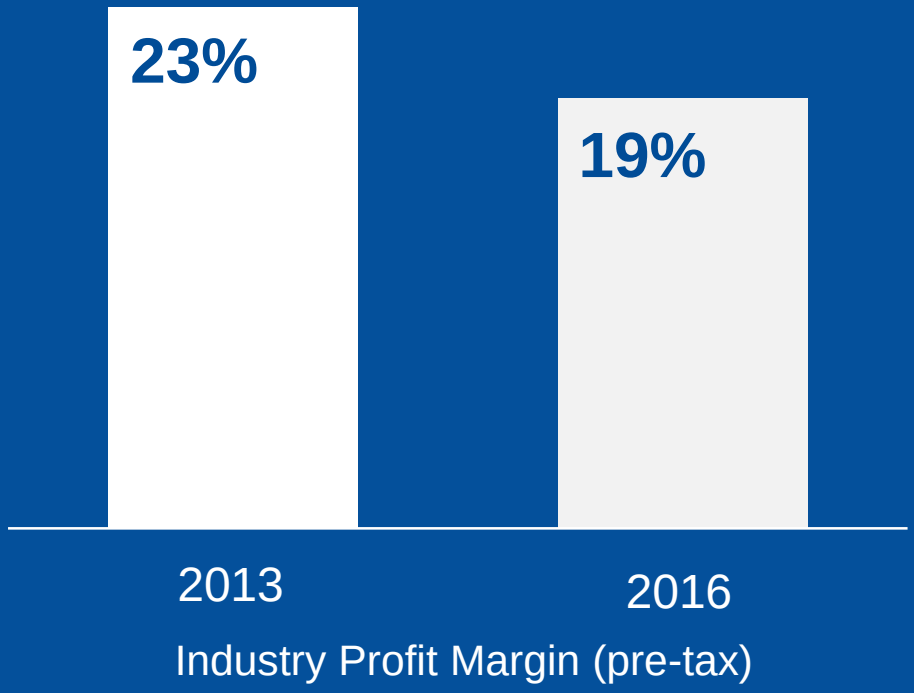
Profitability under pressure



▲ Positive Drivers

- Innovation
- Ageing
- Broader access

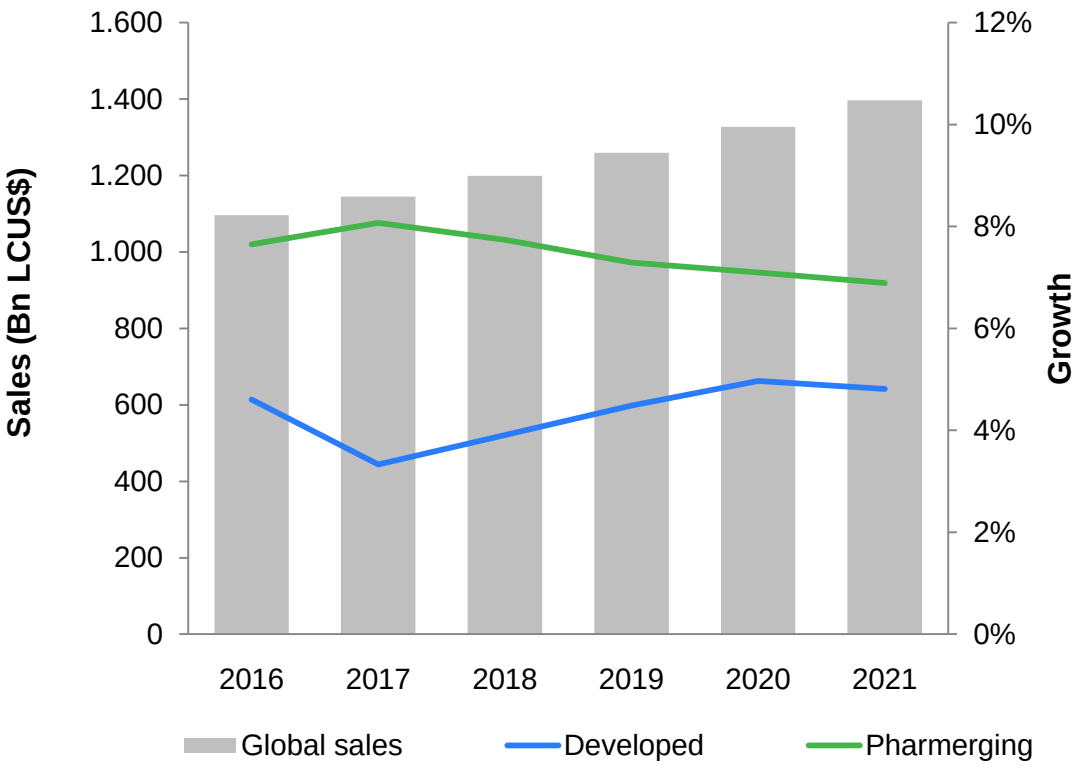
▼ Negative Drivers

- Funding for innovation
- R&D costs
- Commercial complexity

Helped by the US, Global pharma to grow at 3-6% CAGR to $1.4tn by 2021

Global sales and market growth

Forecast 2016-2021



CAGR 2016-21	
Developed	**2-5%**
US	4-8%
Japan	(-1)-2%
Germany	2-5%
UK*	2-5%
France	1-4%
Italy	2-5%
Spain	1-4%
Canada	2-5%
Pharmerging	**6-9%**
China	6-8%
Brazil	6-8%
India	10-13%
Russia	7-9%
Turkey	10-13%
Mexico	3-6%

Higher than region CAGR
On par with region CAGR
Lower than region CAGR

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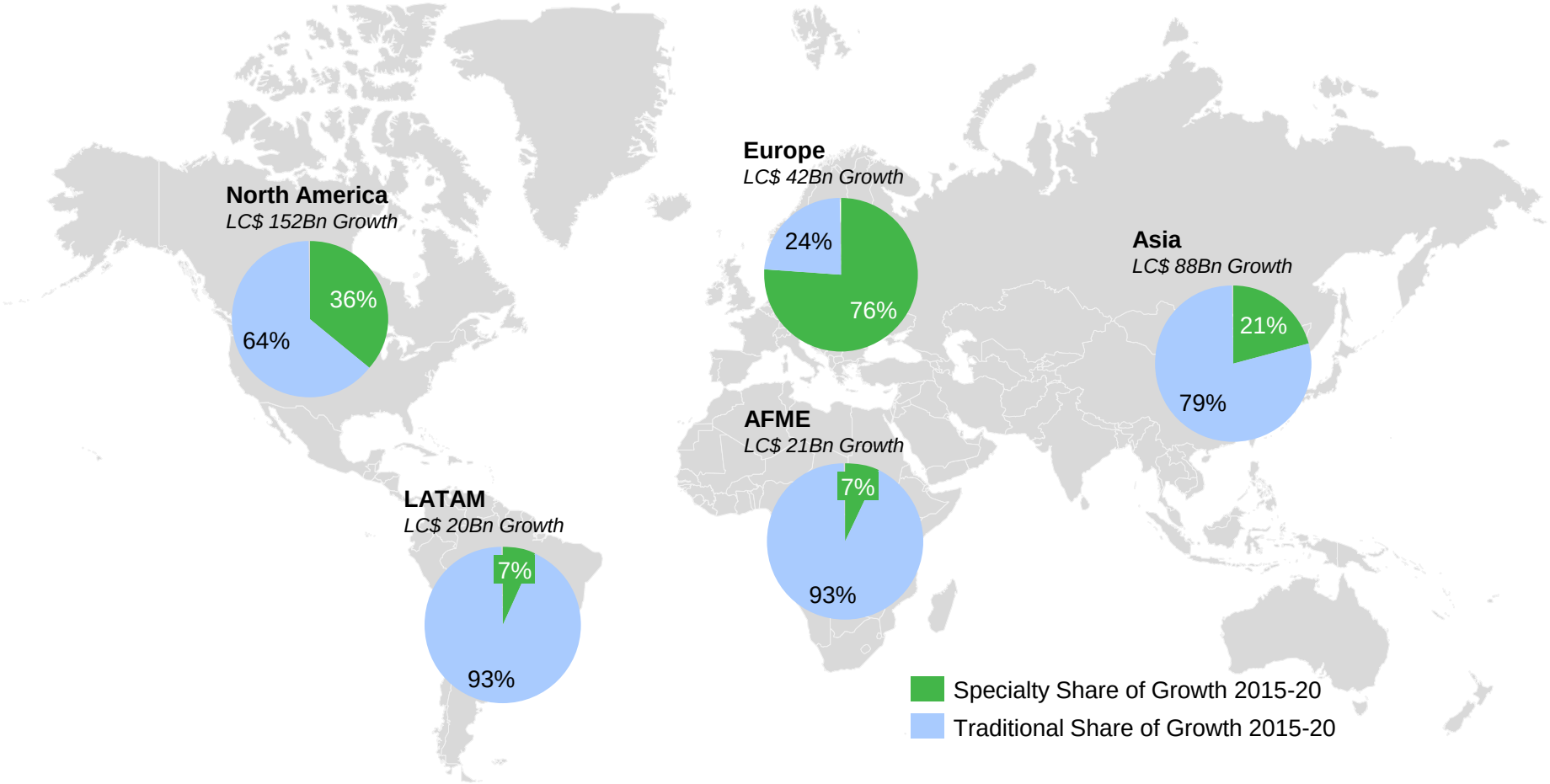
Notes: *Subject to PPRS rebate; Ex-manufacturer price levels, not including rebates and discounts. Contains Audited + Unaudited data; Growth considered on par if the there is overlap between country and region CAGR ranges
Source: QuintilesIMS Market Prognosis Q1 2017

Growth driver in the developed markets is the shift towards specialty medicine

Share of absolute growth by region

Forecast 2015-2020

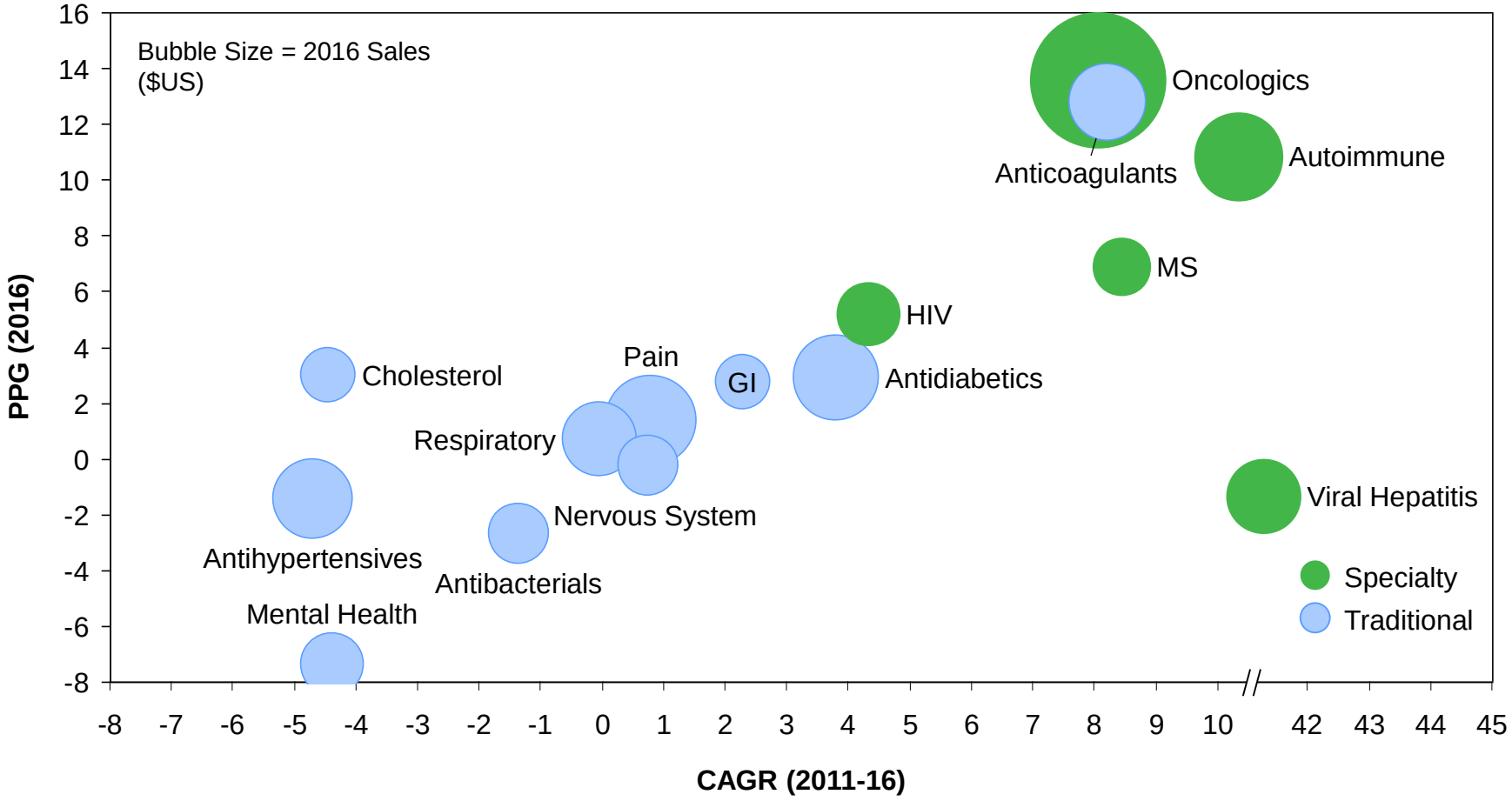


Source: QuintilesIMS Market Prognosis Q3 2016; at ex-manufacturer price levels, not including rebates and discounts.
Contains Audited + Unaudited data; IHII analysis

European growth dynamics are mainly driven by 5 therapy areas

Top 15 Therapy area growth dynamics

Europe 2011-2016

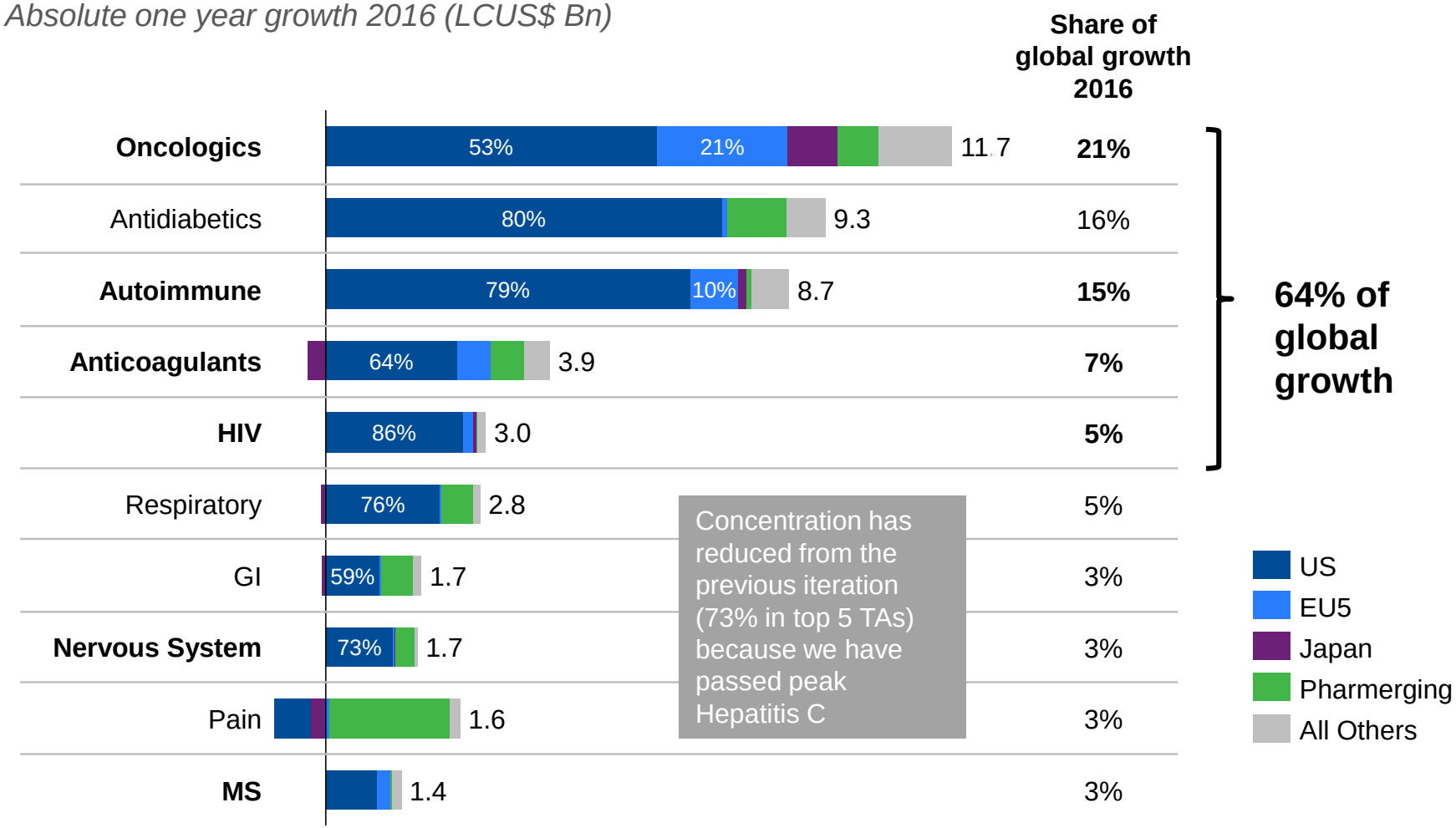


Source: QuintilesIMS MIDAS MAT Q4 2016;CAGR(compound annual growth rate) given is 5 year, PPG = Previous Period growth (growth to the same period of a previous year)

Over 60% of global growth comes from five TAs, four specialty

Global - Highest growth Therapy Areas

Absolute one year growth 2016 (LCUS$ Bn)

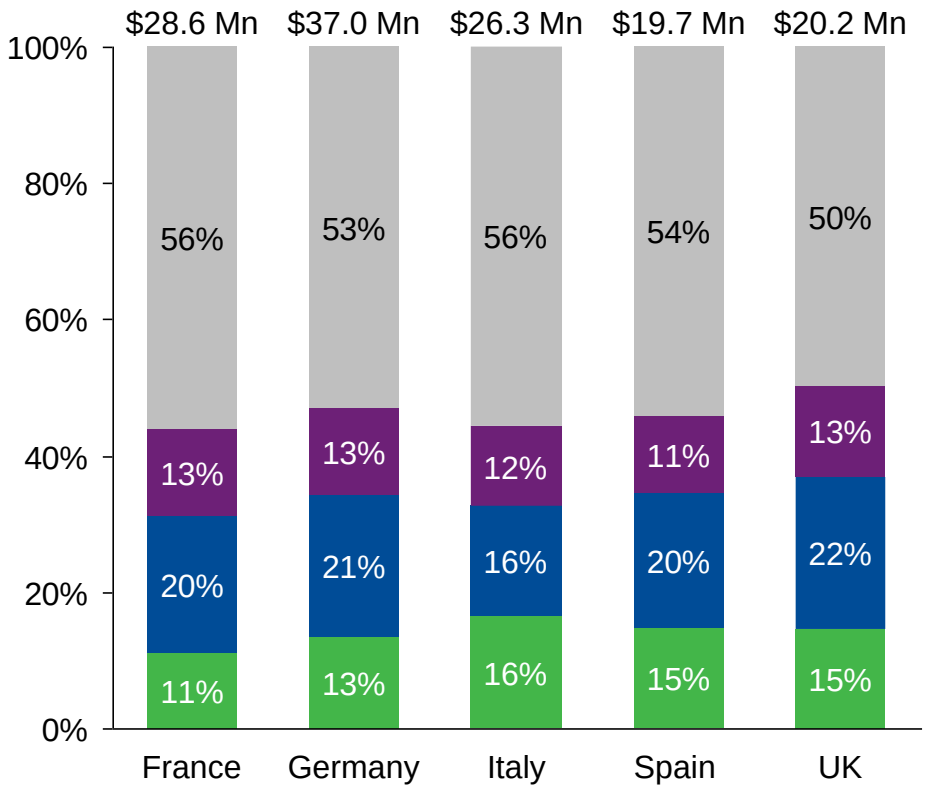


Source: QuintilesIMS, MIDAS MAT Q4 2016, Rx only

Concentration is not only given on TA but also on product level

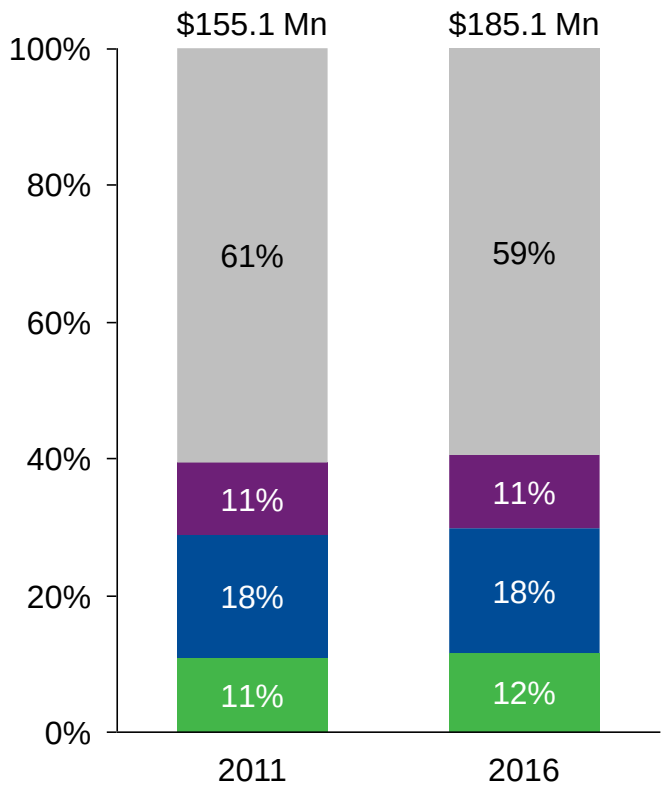
Concentration of product sales

EU5 2016



Concentration of product sales

Europe 2011 vs. 2016



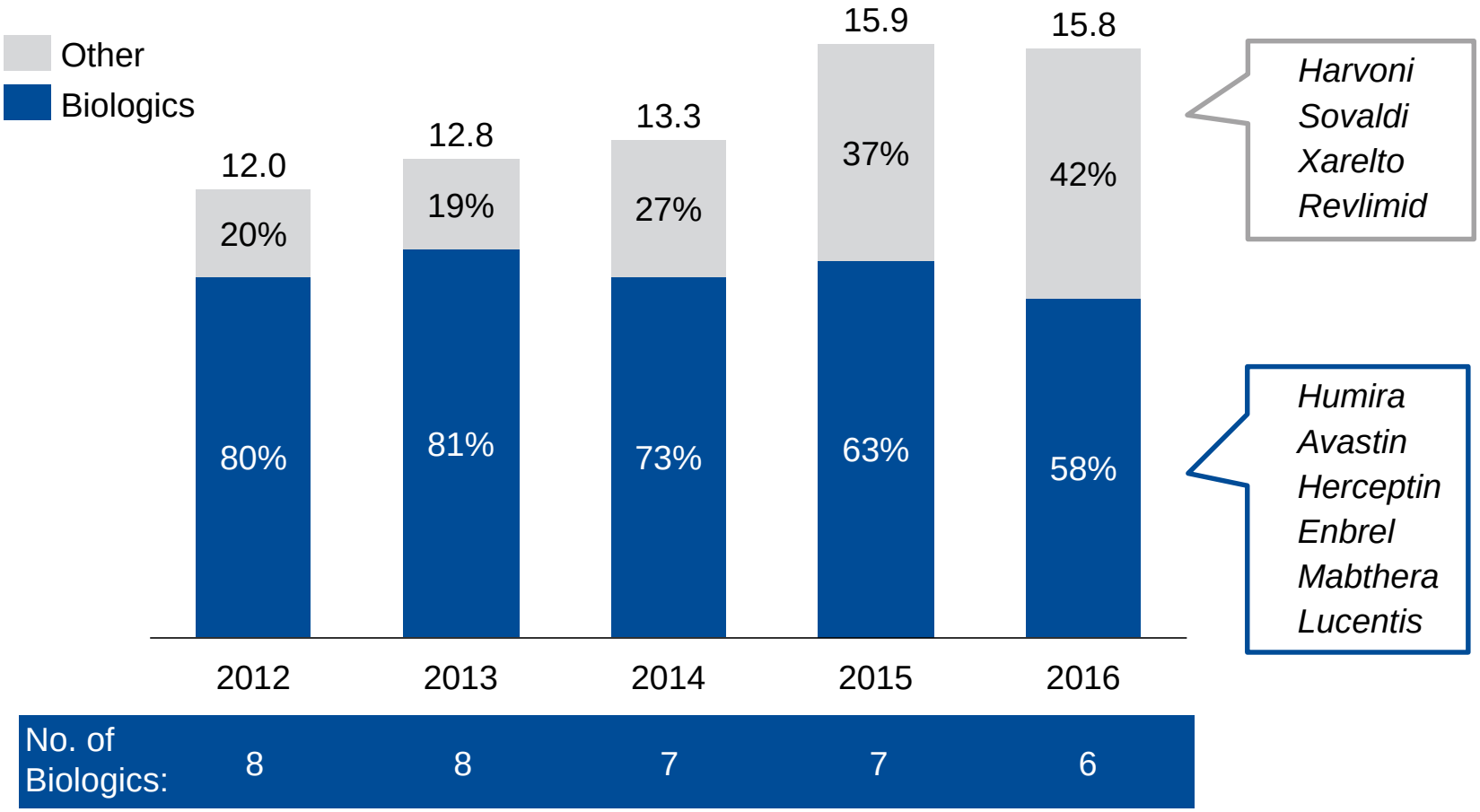
Top 10 products | Products 11-50 | Products 51-100 | All others

Source: QuintilesIMS, MIDAS Restricted, MAT Q4 2011-Q4 2016, Rx only.

High costs in Europe are driven by importance of biologic therapies

Biologics share of Top 10 products sales

EU5, Bn. LCUS$, 2012-2016

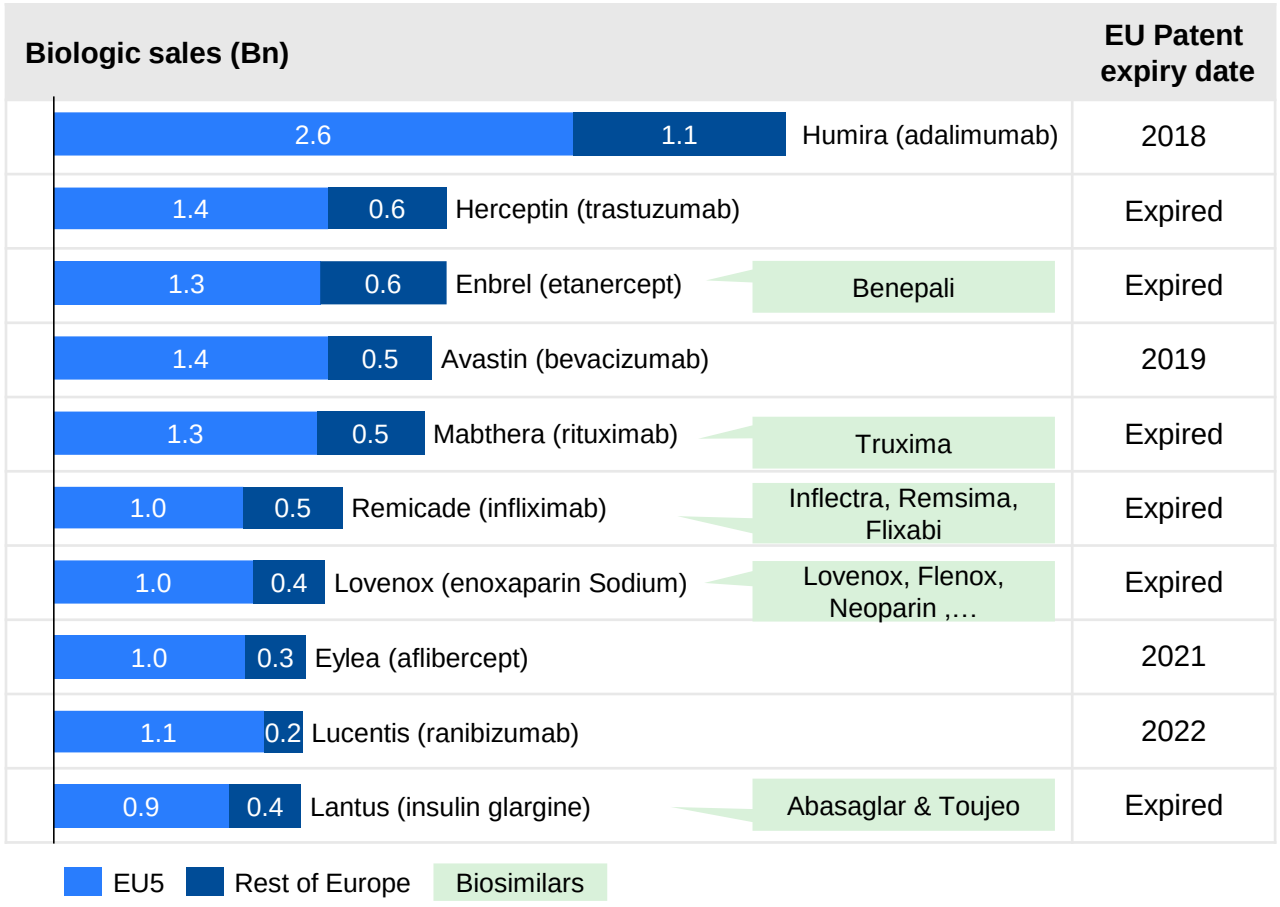


Source: QuintilesIMS MIDAS Q4 2016, Rx only

Important biologics already lost or are about to lose exclusivity which drives biosimilar interest

Europe Top 10 biologics sales by region

LCUS$ 2016



Half of the top biologics have lost protection in Europe, but not all have biosimilars

Biosimilar delay factors:

- Cost
- Complexity in development
- Patent uncertainty
- Regulatory difficulties and uncertainties

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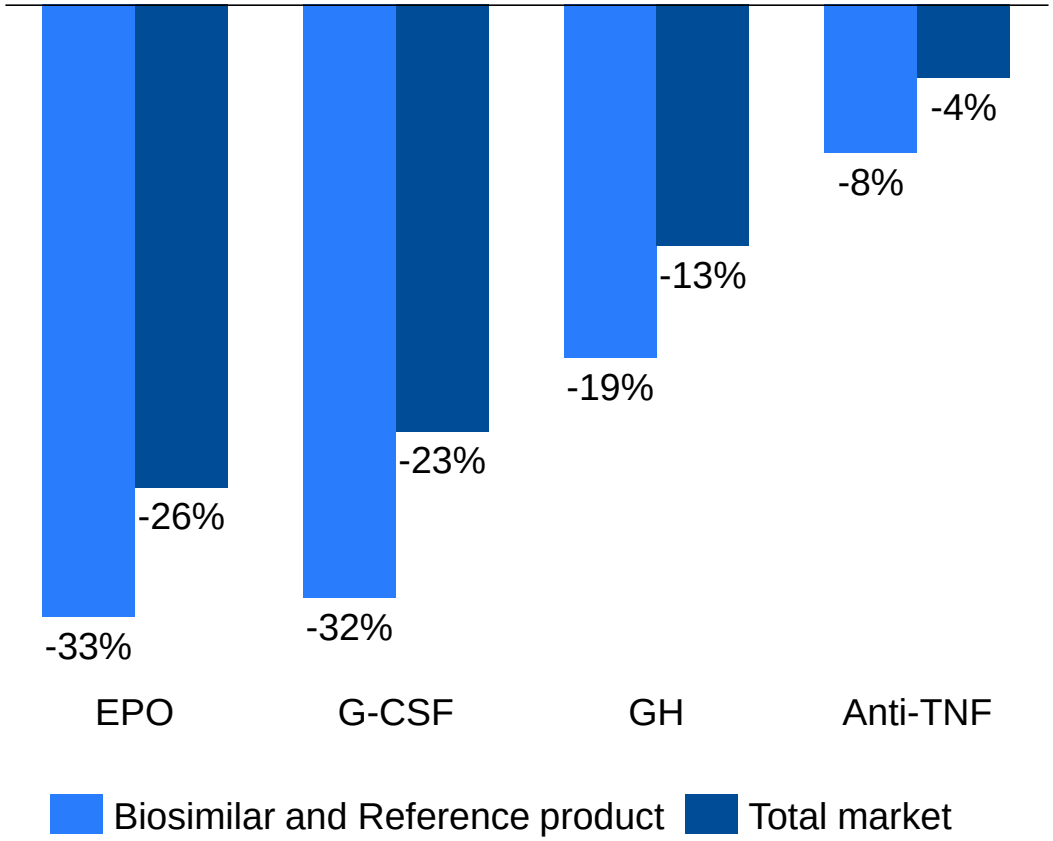
Source: QuintilesIMS MIDAS Q4 2016

The entrance of biosimilars leads to a decrease in prices – putting the originator under pressure

Price reduction

Price per treatment day 2015/year before biosimilar entrance

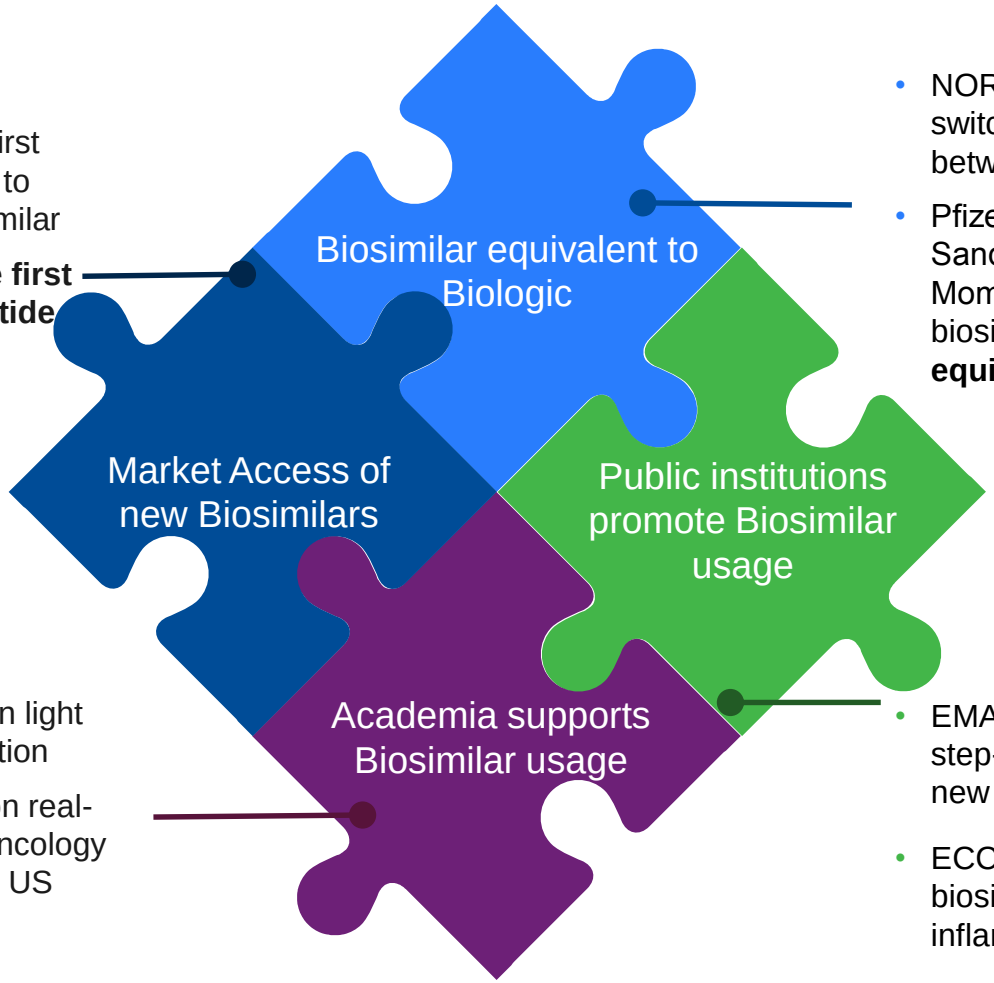


- The increased competition affects not just the price for the directly comparable product but also the price of the whole product class
- The countries with the highest reduction (e.g. Bulgaria, Portugal, Slovakia, Poland, Slovenia) show reduction of 50-70%
- Caveat – prices used in the study are list prices. It can be assumed that additional discounts have been agreed in certain situations

Source: IMS Health (2016): The Impact of Biosimilar Competition ; European Economic Area (EEA)

Latest developments show that the options for biosimilars to replace biologics increase

- South Korea becomes first highly regulated market to approve rituximab biosimilar
- EMA poised to **approve first biosimilars of teriparatide**



- NOR-SWITCH study and Triple switch study **show equivalence** between biosimilar and biologic
- Pfizer's trastuzumab biosimilar, Sandoz's rituximab biosimilar & Momenta's adalimumab biosimilar for psoriasis **show equivalence** to biologic

- JAMA Editors endorse trastuzumab biosimilar in light of Phase 3 data publication
- Major European study on real-world experience with oncology biosimilars welcomed in US

- EMA to pilot tailored advice on step-by-step development of new biosimilars
- ECCO **endorses switching** to biosimilar infliximab in inflammatory bowel disease

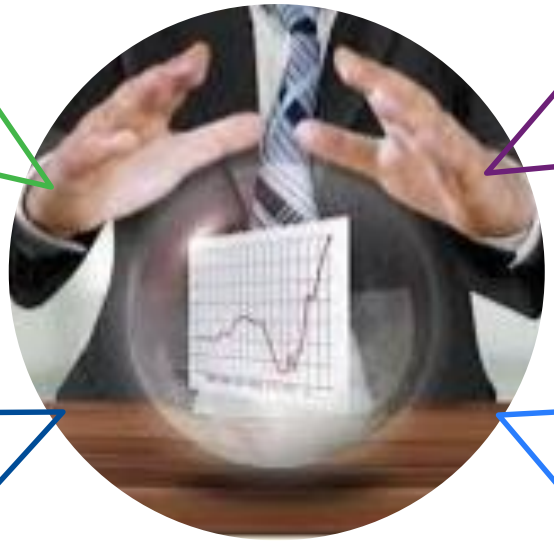
What does the Crystal Ball say about the future of biosimilars?

Policy

- Regulatory developments generally favour biosimilars but 'naming' and 'patent information exchange/linkage' remain challenges

Price

- In the absence of any other differentiators biosimilar selection is driven by price – they are taking the route of small molecule generics
- Increasing competition and the dynamics of multi-sourced products will allow payers stronger negotiating options



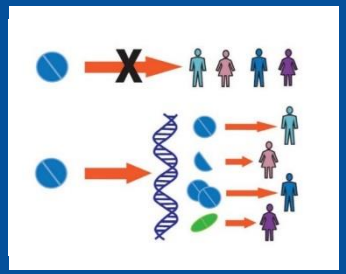
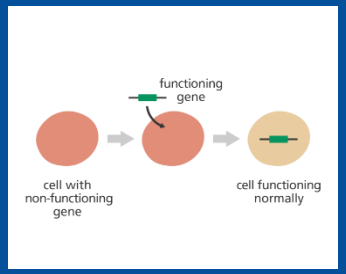
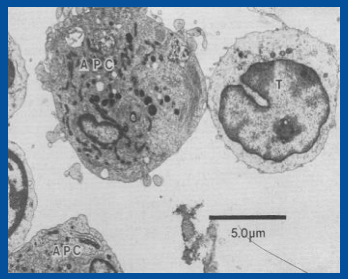
Acceptance

- Savings and patient access will drive acceptance of next wave of biosimilars
- Positive studies and experience will drive broad adoption of biosimilars by physicians

Usage

- Adoption of substitution rules may parallel use of generic medicines
- Procurement methods will speed up uptake and increase price differentials
- Awareness and usage of biosimilars across varying therapeutic areas will accelerate biosimilar usage

Biosimilars offer payers savings, however growth in complex specialty therapies driving up the cost per patient

Personalised Medicine	Orphan drugs	Large patient population therapies e.g. Alzheimer's	Gene therapies	Cell therapies
				

Source: QuintilesIMS

As the healthcare industry increasingly scrutinizes drug costs, it is also questioning the value of innovation

Bloomberg Markets Tech Pursuits Politics Opinion Businessweek

Trump's Drug-Price Stance Puts Pharma on Notice

by Anna Edney and Zachary Tracer
12 January 2017, 17:59 GMT Updated on 12 January 2

BRIEF

New anti-PD1 drugs overpriced, ICER says

Cancer : le débat monte en France sur le prix des médicaments

CATHERINE DUCRUET | LE 03/02/16 À 18H00

Cancer: the debate grows about the price of drugs in France

L'appel de 110 cancérologues contre le coût des traitements

The appeal of 110 oncologists against the cost of treatments

Farmaci che costano miliardi. Le Big Pharma rispondono: "Senza profitti non c'è ricerca"

Drugs which cost billions – Big Pharma responds, "without profit, there is no research"

Farmaci malattie rare, profitti esagerati?

Do medication for orphan diseases bring in exaggerated profits?

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Source: QuintilesIMS

Payers in Europe are increasing focus on managing pharmaceutical prices and affordability

Controlling Costs

Price negotiation collaboration and net price transparency

- Netherlands and Belgium announced pilot collaborative price negotiations for orphan drugs
- Greek and Portuguese health ministers call for increasing payer collaborations

Post launch payer led RWE scrutiny

- France NOAC re-assessment based in part on own RWE
- Italy and France Avastin reimbursement for use in AMD
- Infliximab switching NOR-SWITCH

Budget caps and pharma payback schemes

- Portugal and Italy reviewing payback mechanisms for budget overspend
- French HCV spending cap
- UK PPRS scheme

Increasing emphasis on drug cost-value

- NHS England Cancer Drugs Fund being included under NICE QALY assessment
- NICE QALY cost-effective threshold being reviewed
- Italian and French MoH reviewing current drug reimbursement systems

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Source: QuintilesIMS

Cost pressure pushes European collaborative purchasing efforts

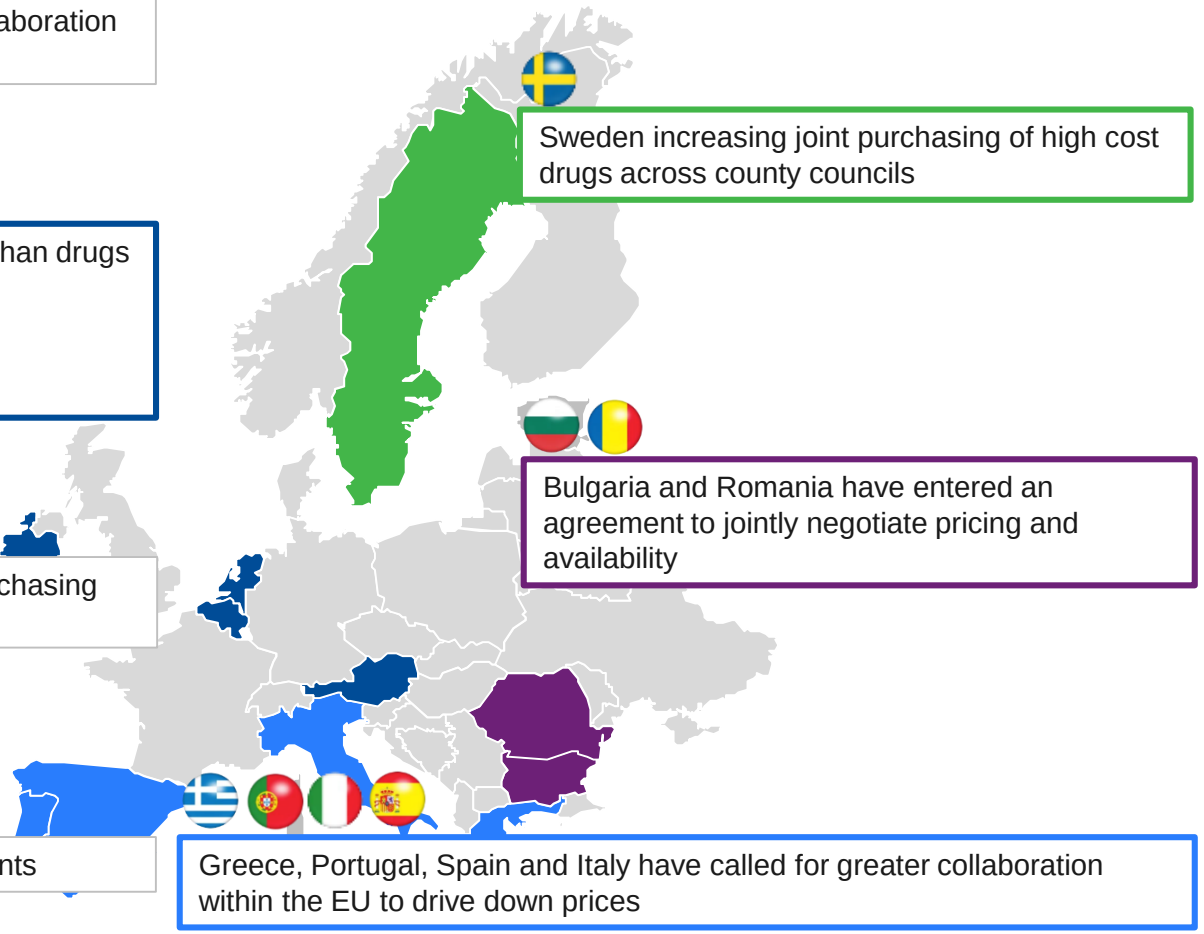
EU commission exploring EU wide pharmaceutical price control measures, centred around collaboration and price transparency

Joint purchasing agreement focused on Orphan drugs

- Pioneered by Netherlands and Belgium
- Joined by Luxembourg and Austria
- Ireland announced it would join

Dutch insurers introducing joint hospital purchasing schemes for biologics

Italy restricting confidential pricing agreements



Sweden increasing joint purchasing of high cost drugs across county councils

Bulgaria and Romania have entered an agreement to jointly negotiate pricing and availability

Greece, Portugal, Spain and Italy have called for greater collaboration within the EU to drive down prices

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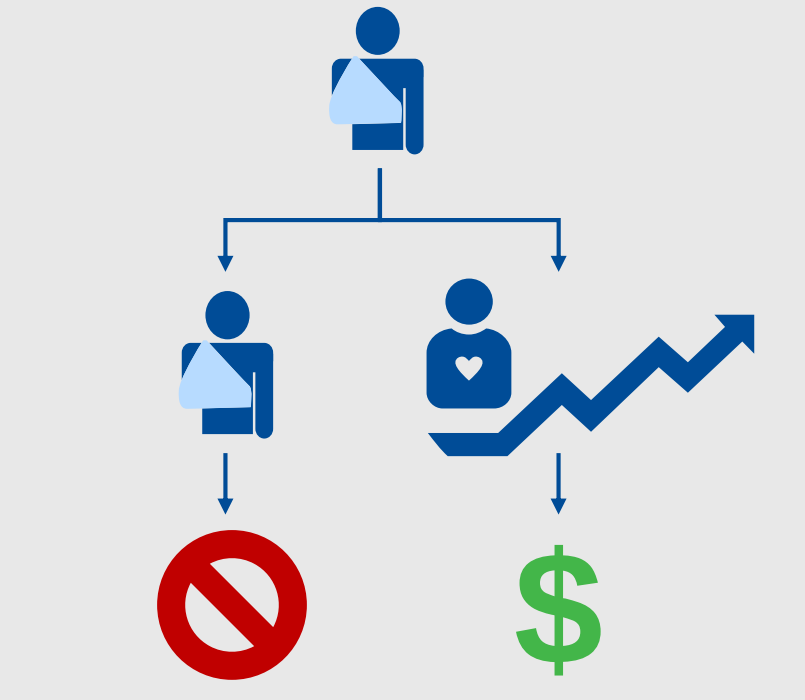
Source: QuintilesIMS

Innovative pricing models are becoming more prevalent such as pay-for-performance…

Pay-for-performance

Payer only pays if patient meets pre-agreed upon clinical outcomes



Description	Product value and associated price is assessed based on performance across endpoints, level of patient response, and/or performance on specific metrics as demonstrated by clinical trial endpoints or RWE
List-Price	Different prices for the same substance based on the prescription (subgroup)
Process	Agreements for each Subgroup
Examples	• Overall Survival • Progression-Free Survival • Reduced Hospitalizations • Identifying patient responders with recommended pre-test

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Source: Feasibility and attractiveness of indication value based pricing in key EU countries, Journal of Market Access & Health Policy

…and indication-based pricing

Indication-based pricing

Price determined by comparing efficacy across indications for a single product

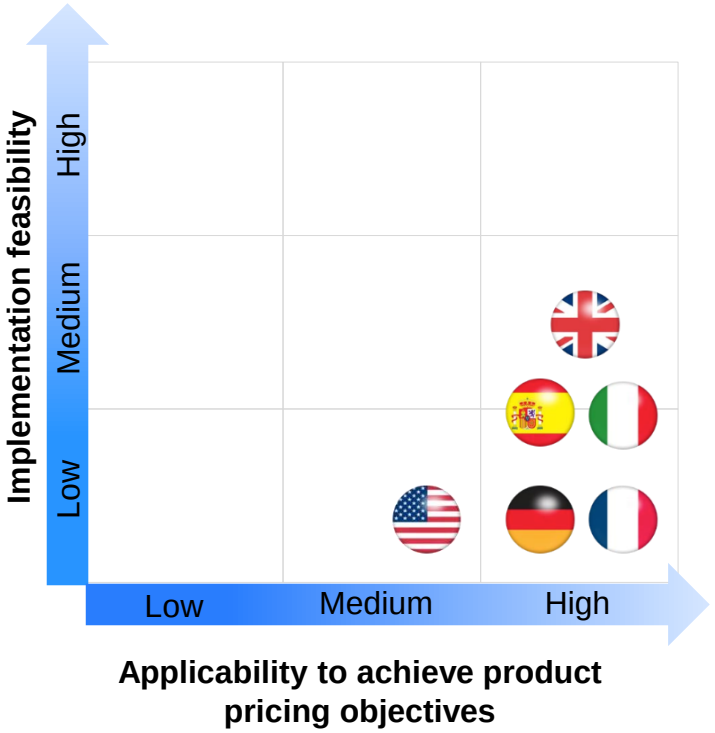
Description	Payer pays different prices by indication for a specific therapy based on volume, value, and clinical outcomes assessment
List-Price	One price for one product
Process	Weighted price based on estimated patient pops
Examples	• Avastin use in NSCLC and breast cancer • Humira use in RA and Crohn's disease (CD)

Source: Feasibility and attractiveness of indication value based pricing in key EU countries, Journal of Market Access & Health Policy

Pay-by-use schemes can provide win-win scenarios, but not everyone is ready

Pay-by-use implementation challenges across key US and EU markets

Applicability and Feasibility matrix



- PbyU would need to be layered on top of AMNOG price negotiations which is not possible today
- No experience with registries; implementation could delay pricing negotiations
- Data per indication at patient level would be challenging to collect
- Concerns raised on legal and implementation feasibility; however, registries are already in place
- Existing registries may need to be linked and incentivised for data entry must be aligned
- Challenging to develop data collection infrastructure and to explain variable coinsurance / OOP costs by indication to patients

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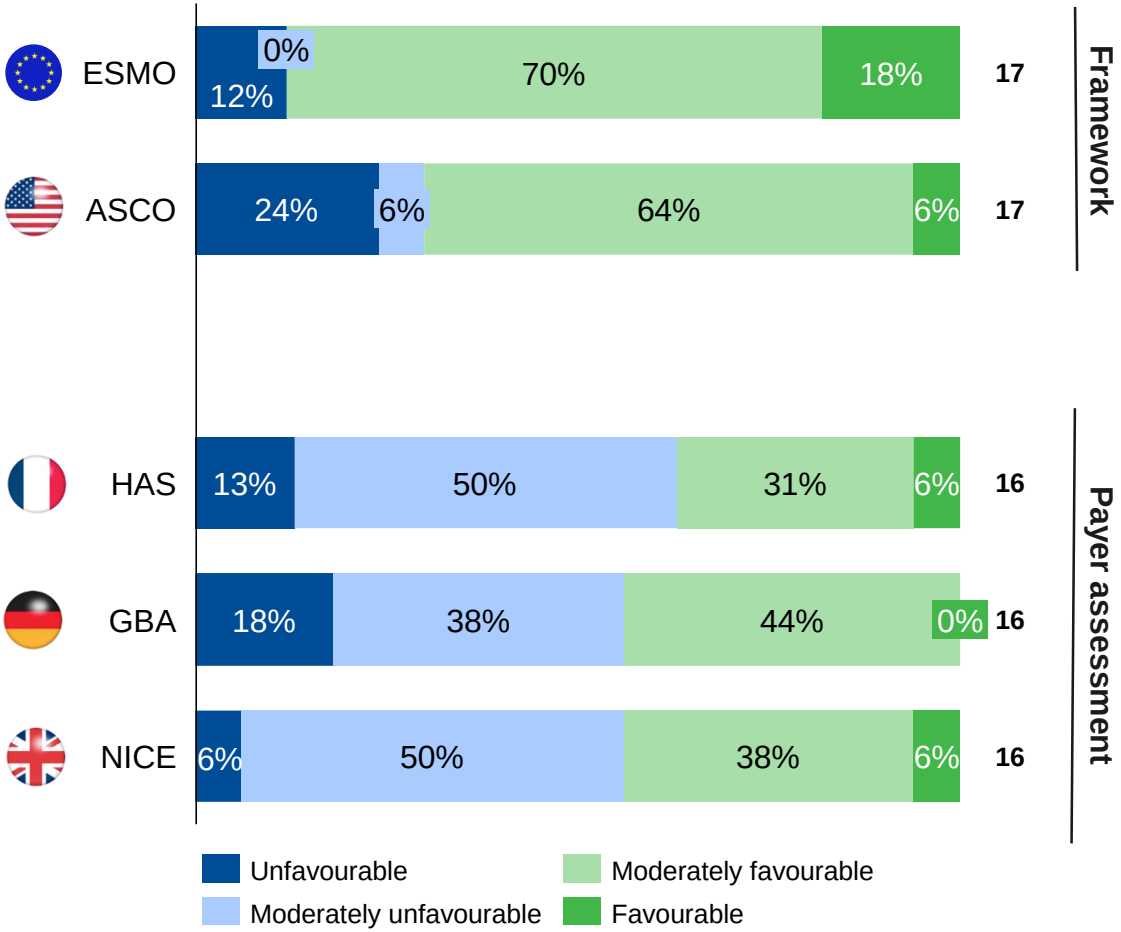
Source: QuintilesIMS

The development of value frameworks aims to shake up current practice, but is value defined in the same way?

Value assessment

Framework vs. EU payer evaluation



- Considering only products with all assessments available, the frameworks tend to produce more favourable scores than payer assessment
- ~90% of trails produce favourable scores with the ESMO value framework, whereas only 35-50% of payer assessments are favourable

Source: QuintilesIMS PMA 2016

Also comparing HTA assessments reveals considerable discrepancies

Selection of oncology products: HTA assessment ratings

Brand name	HAS	GBA	NICE
Jevtana	ASMR III	2	✗
Halaven	ASMR IV	4	✗
Yervoy	ASMR IV	1	✓
Zytiga	ASMR III	1	✓
Zelboraf	ASMR III	1	✓
Inlyta	ASMR IV	2	✓
Xalkori	ASMR III	3	✗
Perjeta	ASMR III	3	✗
Tafinlar	ASMR V	5	✓
Xtandi	ASMR III	1	✓
Zaltrap	ASMR V	-	✗
Erivedge	ASMR IV	4	✗
Kadcyla	AMSR II	1	✗
Opdivo	ASMR III	1	✓
Keytruda	ASMR II	1	✓
Stivarga	AMSR IV	4	✗

Positive unanimous agreement*

Negative unanimous agreement*

*ASMR or GBA rating of 3 or lower has been classed as positive

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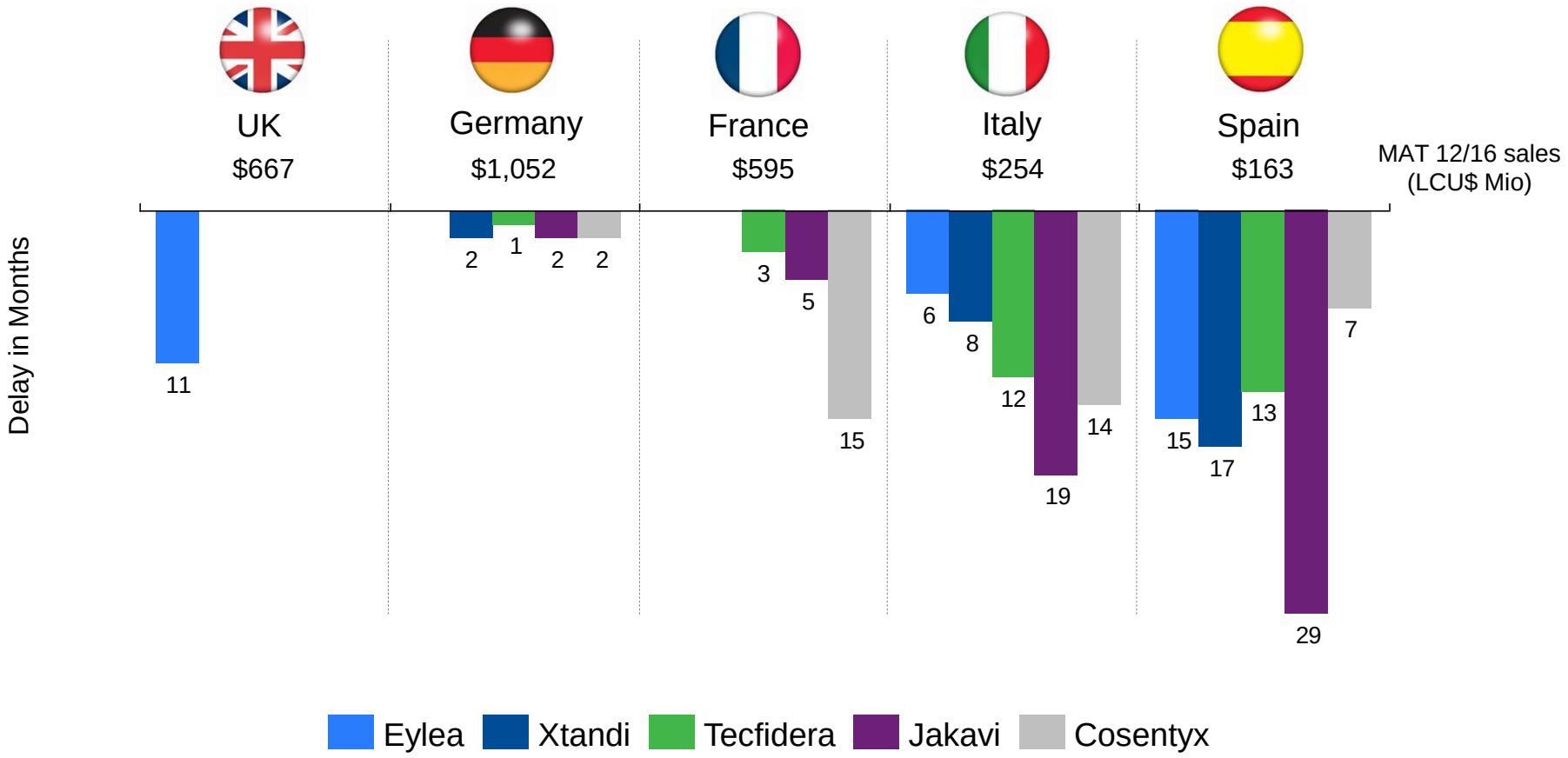
Source: HTA body websites

Payer evaluation influences launch readiness: Rollouts across EU5 diverge greatly

Top 5 drugs delay from 1st country's launch

Launched 2012-2016, EU5

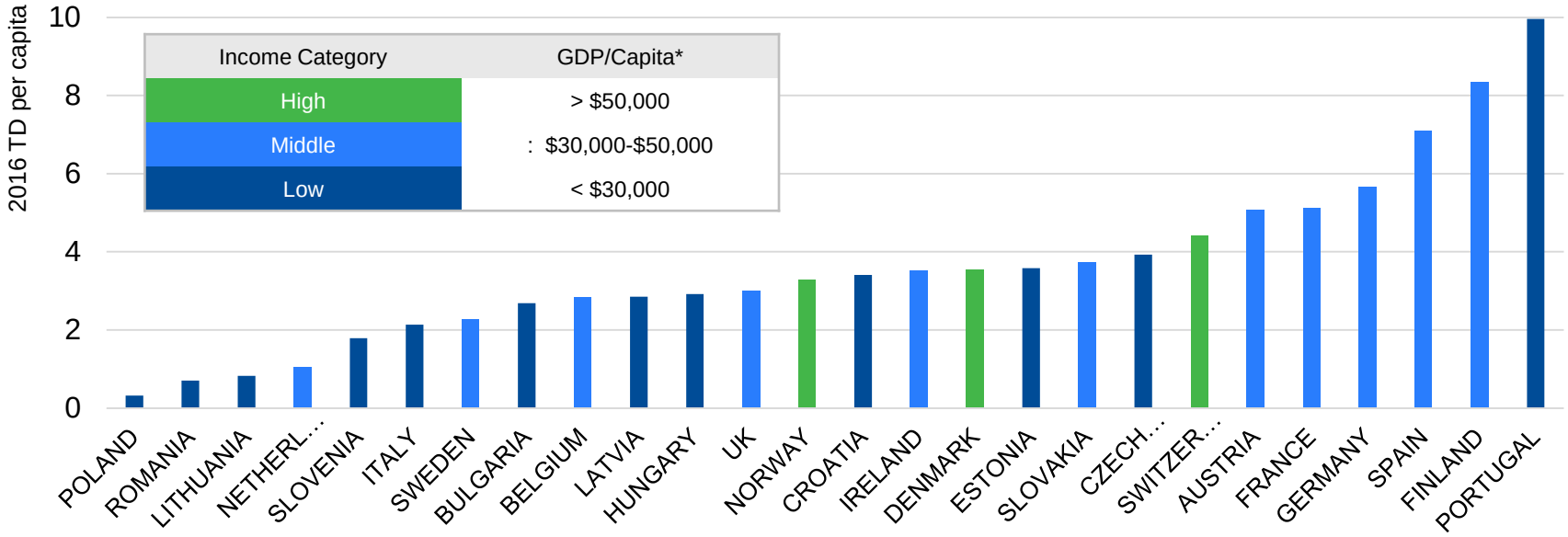


Source: QuintilesIMS MIDAS 12/2016, Rx only. Delay calculated from 1st country's launch in one of the EU5 markets. Country ranked by months of delay since first launch; drugs ranked by sales in EU5.

Looking at innovative anti-diabetics shows very large country differences in uptakes

Uptake of Innovative Anti-diabetics

(DDD/100,000 people) 2016



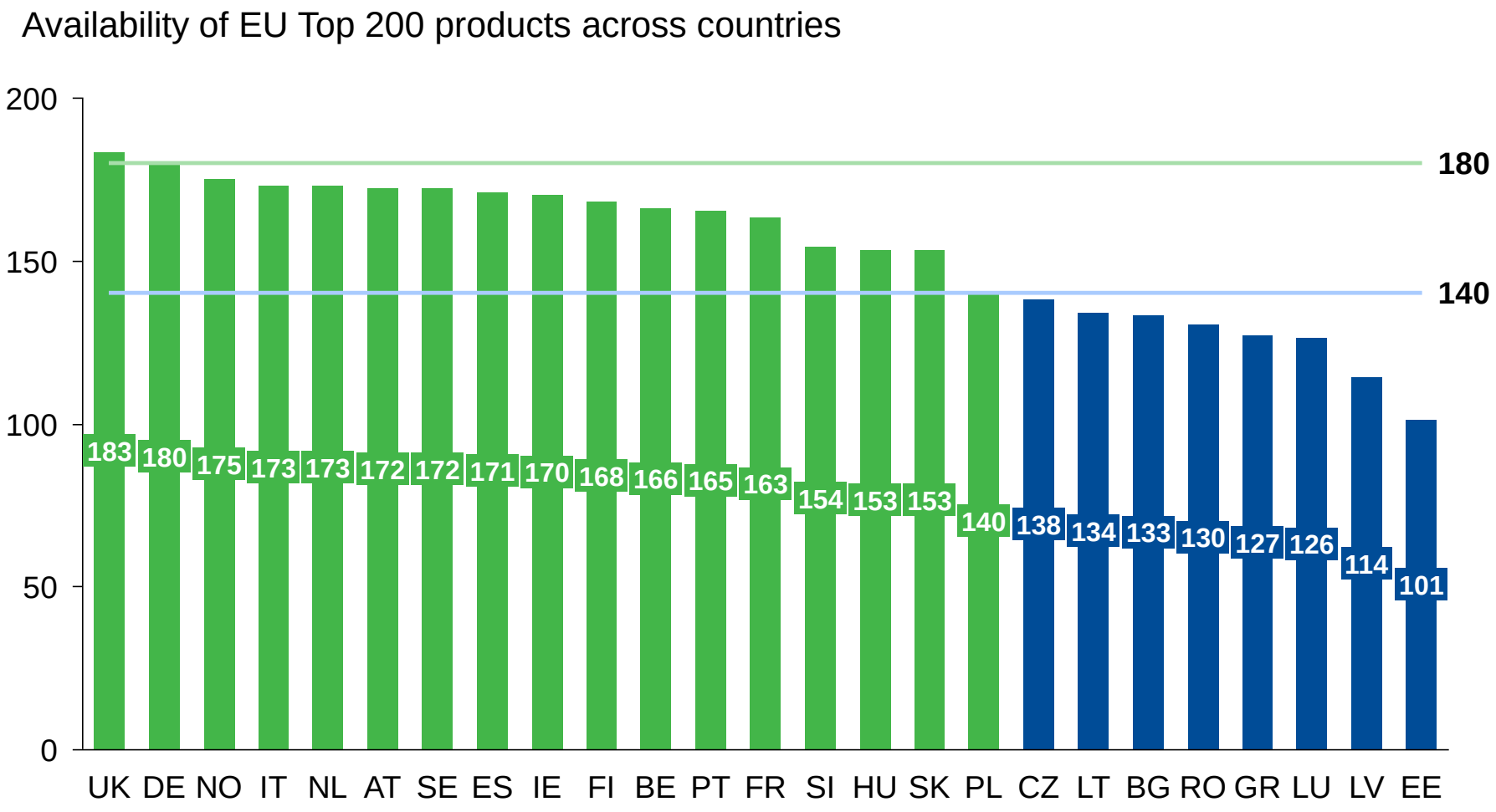
Many factors can affect uptake :

- GDP per capita and the financial situation of the country (high - medium - low income countries)
- Regional decision makers
- Price premium versus existing treatment
- Stakeholder attitude to innovation
- If innovation is funded by the public or private payer

Anti-diabetics includes: ALBIGLUTIDE, ALOGLIPTIN, DULAGLUTIDE, EXENATIDE, LINAGLIPTIN, LIRAGLUTIDE, LIXISENATIDE, SAXAGLIPTIN, SITAGLIPTIN, VILDAGLIPTIN, ALOGLIPTIN#METFORMIN, ALOGLIPTIN#PIOGLITAZONE, LINAGLIPTIN#METFORMIN , METFORMIN#SAXAGLIPTIN , METFORMIN#SITAGLIPTIN , METFORMIN#VILDAGLIPTIN

Source: QuintilesIMS MIDAS Q4 2016, Treatment day calculated using WHO DDD

In most EU countries only 70-90% of the Top 200 products are available



Source: QuintilesIMS MIDAS Q4 2016, Rx only

In the EU, there is a move towards harmonizing technical assessments

Early dialogue with regulatory bodies

Scientific advice in place with regulatory agencies

EUROPEAN MEDICINES AGENCY

eunethta

Move towards **parallel, centralised** Regulatory + HTA advice

Early dialogue with HTA bodies

Individual national HTA advice (e.g. NICE, GBA, AIFA) widely sought

- Provide HTA **advice to** define **relevant evidence and try to accelerate time to access**
- Stakeholders discuss the planned development early, including **patient populations, comparators, trial design, endpoints**

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Source: QuintilesIMS

Currently, EUnetHTA started phase 3 which aims to put joint assessments into real life

Putting the HTA collaboration into practice	*Strengthening practical application of tools and approaches*	*Implementing a sustainable mechanism for HTA cooperation*
Joint Action 1 (2010-2012)	**Joint Action 2 (2013-2015)**	**Joint Action 3 2016 - 2019**
• Put into practice an effective and sustainable HTA collaboration in Europe • Attempt to lower barriers for collaboration • Deliver context specific reporting of HTA results, e.g. new application of the HTA Core Model	• Strengthen the practical application of tools and approaches to cross-border HTA collaboration • Establish a sustainable structure for HTA in the EU • Bringing collaboration to a higher level resulting in better understanding • 15 joint assessments were performed during EUnetHTA JA2 (2012-2015)	• Defining and implementing a sustainable model for scientific and technical cooperation on HTA in Europe • Results of the pilot joint assessments need to be put into the “real life” routine HTA production processes of the EUnetHTA participating organizations.
9 Guidelines 1 Pilot Rapid Relative Effectiveness Assessment (REA)	5 Guidelines 6 (Pharmaceutical) /6 (Medical Devices) Pilot Rapid (REA) 11 Early Dialogues	37 (Pharmaceutical) /43 (Medical Devices) Pilot Rapid (REA) 35 Early Dialogues
Coordinator: Danish Health Authority		**Coordinator: Zorginstituut Nederland (ZIN)**

Impact of BREXIT?

Source: EUnetHTA website

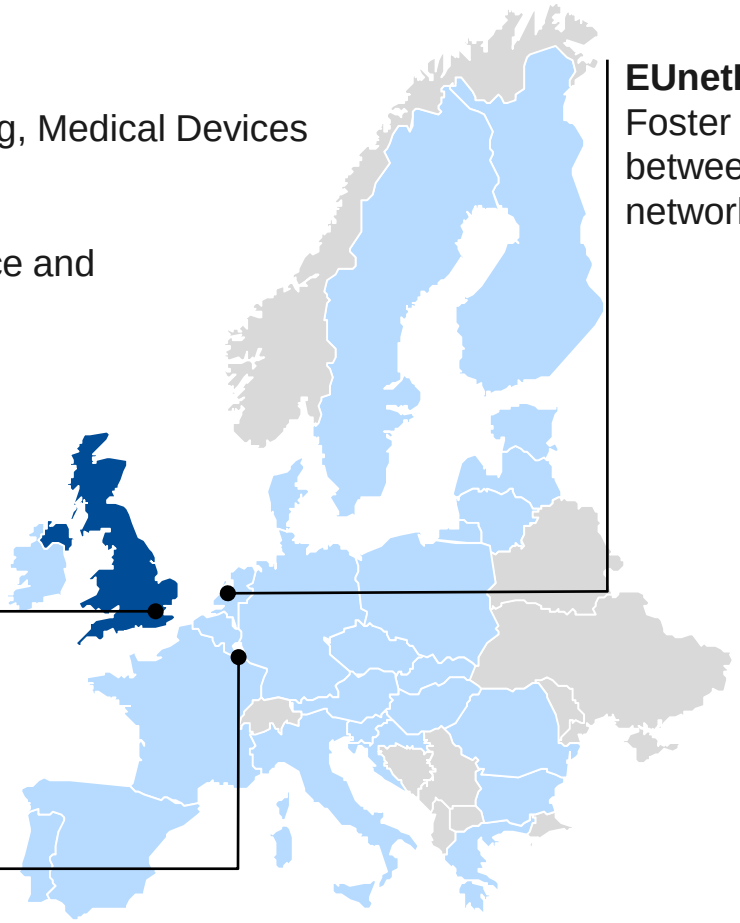
The European pharmaceutical industry's infrastructure is concentrated in UK

EMA
Regulations, e.g. Clinical Trial, Orphan Drug, Medical Devices

EnCePP
Developing standards for pharmacovigilance and pharmacoepidemiology

Unified Patents Court (now ratified)
London branch will cover pharmaceuticals

Falsified Medicines Directive
Pan-European



EUnetHTA
Foster collaboration between European HTA networks

European Investment Bank

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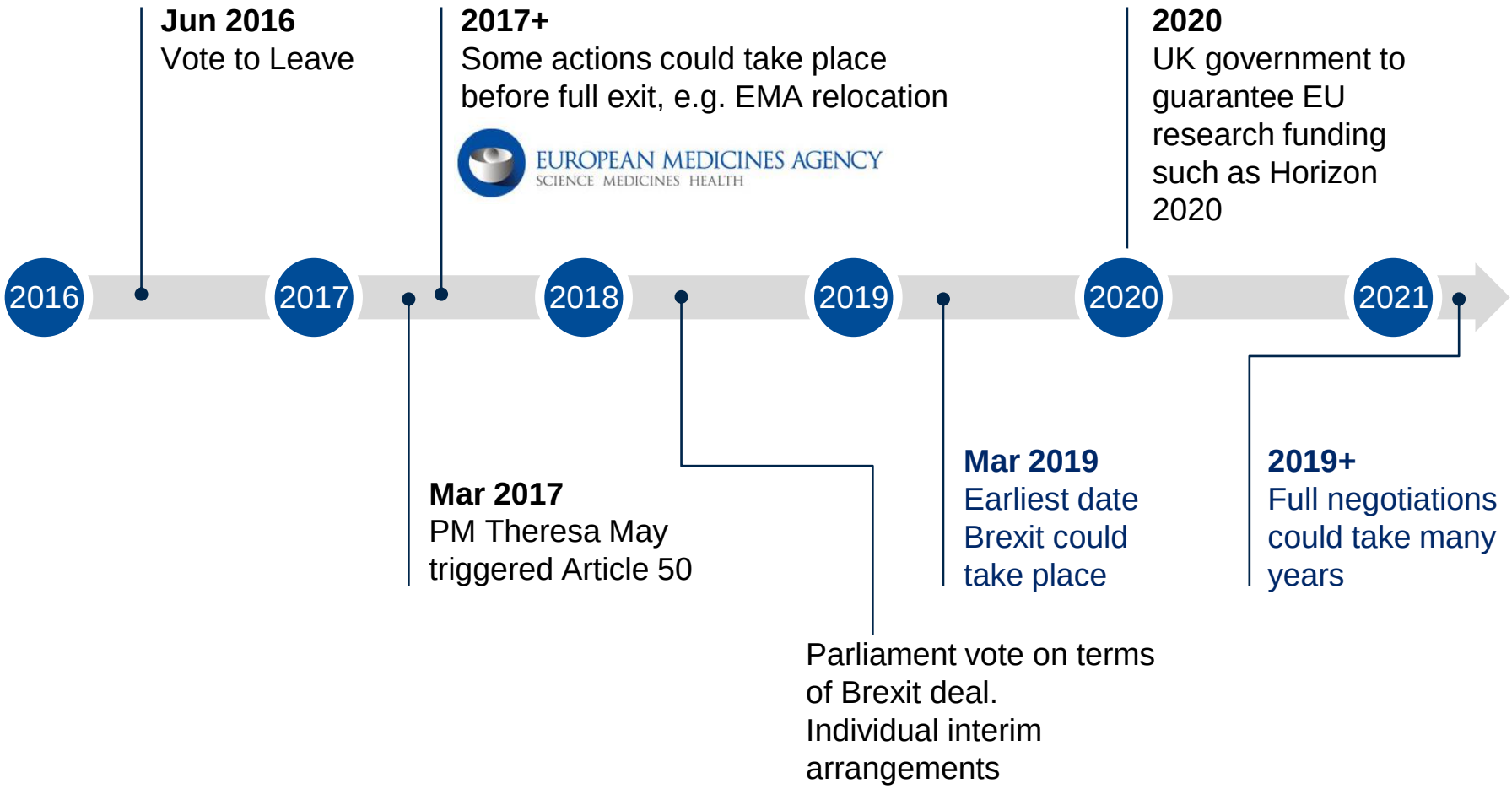
Source: QuintilesIMS

Brexit timeline: slow and difficult – much uncertainty remains



Source: QuintilesIMS

Four key areas of uncertainty for the pharmaceutical industry

Regulatory

- Future location of the EMA and the future relation of the MHRA to it
- Distribution, Pharmacovigilance and Clinical trials regulation are among many areas which could be impacted
- European Patent system; Pharma Branch of the Unified Patents Court will be sited in London as planned

Trade

- Sterling devaluation shifts balance of pharmaceutical trade, although UK remains a net pharmaceutical importer
- Impact of creeping regulatory dissonance on trade?

Commercial

- Concerns about location and freedom of movement of highly international pharmaceutical industry employees
- Increased divergence / complexity in harmonized structures supporting pharmaceutical business
- Possible impact on launch sequence across Europe for novel drugs

Scientific

- Uncertainty on post-2020 position with respect to key EU scientific funding; Theresa May announces £2bn of extra funding for science by 2020 much of which will go to biotech
- Barriers to movement of highly skilled labour
- Barriers to international cooperation on policy, research and other crucial scientific areas

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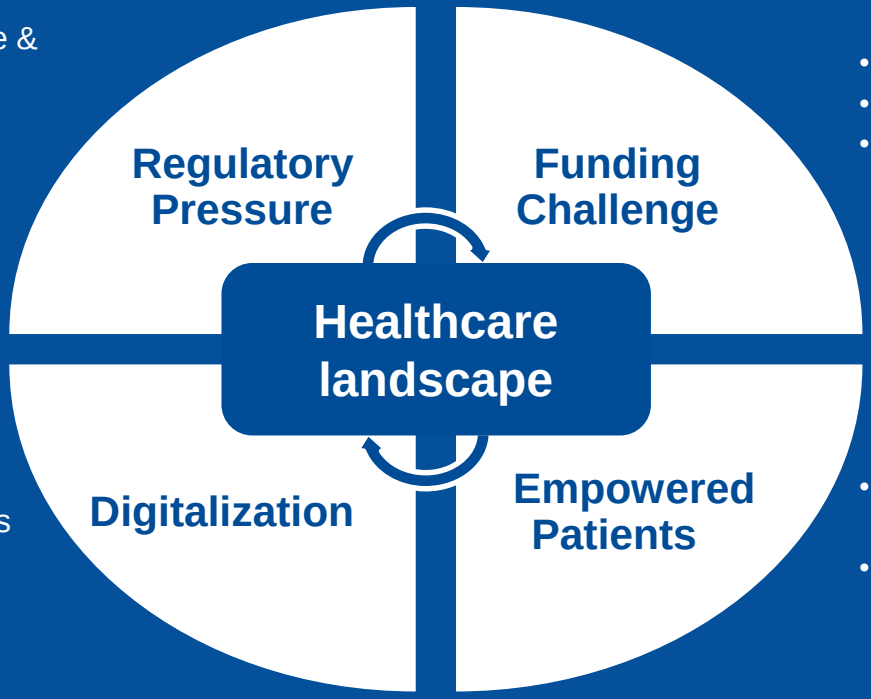
Source: QuintilesIMS

Not only drug market is getting under pressure MedTech landscape is transforming too

- Focus shifts from price to value & risk sharing
- Advanced clinical study design
- Product safety
- Anticorruption & Transparency



- Hospital chains
- Sick fund mergers
- Out-of-pocket-spend

- New products with access to data, networks and providers or intermediaries
- Internet of things

- Informed patients drive demand
- Co-payment drives choice

Source: QuintilesIMS

New regulations will create stronger regulatory institutions and stricter formal requirements

Manifestation of Regulatory Pressure	Implications
Focus shifts from price to value & risk sharing (HTA)	• Increasing power of authorities who assess the benefit of new, innovative diagnostic and treatment methods • New risk share models for reimbursement for financing • "Me-too" and "me-better" products will no longer achieve premium prices
New high-risk class medical devices have to pass benefit assessment for reimbursement in inpatient sector	• Need for demonstration of additional value in mortality, morbidity or quality of life (QoL) via RCTs and in comparison to appropriate comparative intervention • Failure of benefit assessment limits funding possibilities • Meeting formal requirements means increased investments in time and money
Increased formal requirements on product safety & performance (EU Medical Device regulation)	• Need for long-term efficacy and safety data (OBS, RETRO, Registers, Predictive Analytics') • Implement registers for new products/indications • Post-market surveillance and introduction of new unique device identification
Anticorruption & Transparency	• Transparent funding strategies and KOL listing • Disclosure of clinical data • Information system to medical doctors
Harmonization of national HTA legislation within EU	• Outcome of benefit assessment in Germany impacts reimbursement in other EU countries

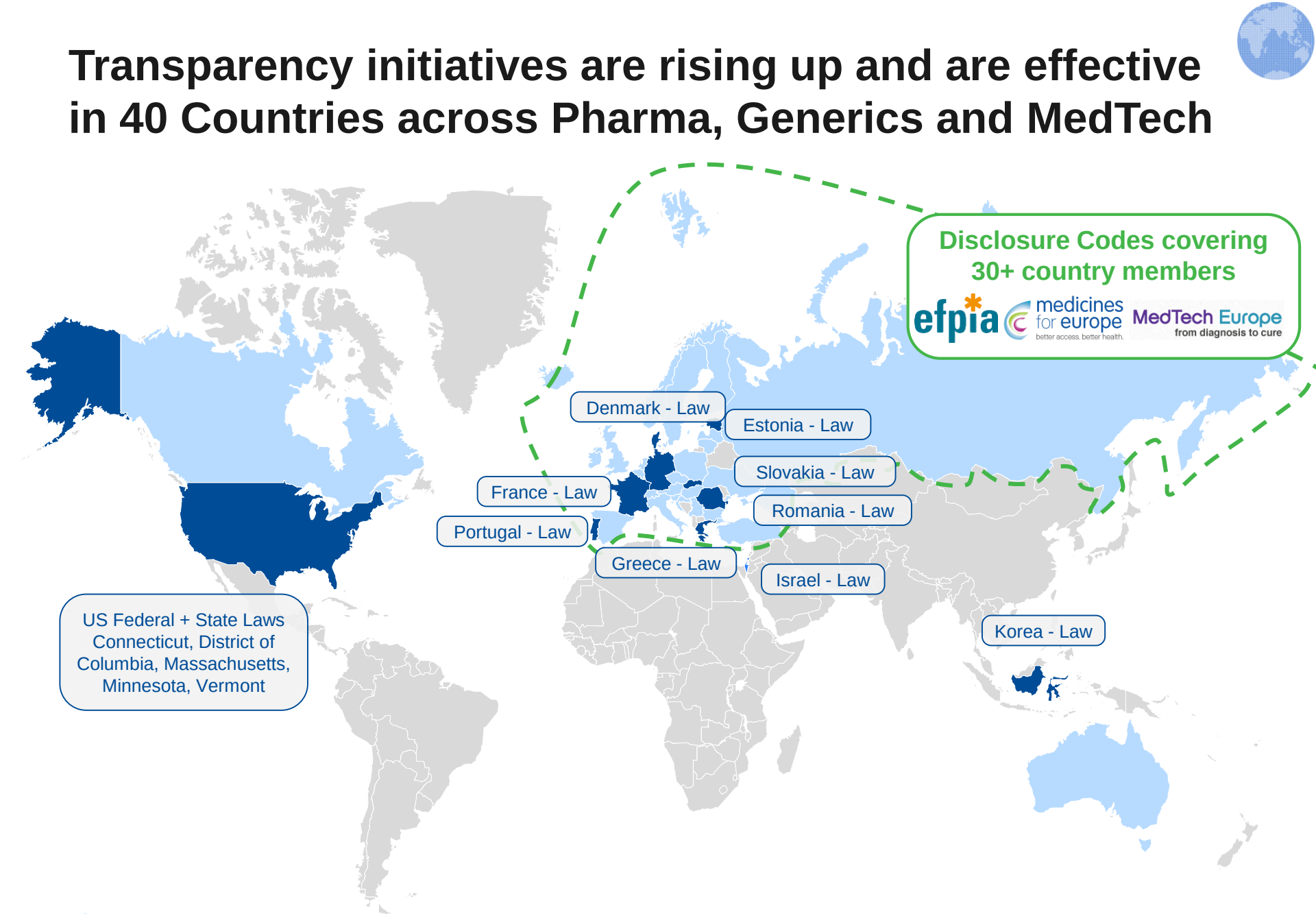
Impact on MedTech players

- Need for high level short- and long-term clinical evidence, advanced study design
- MedTechs face new strong decision makers (e.g. IQWIG)
- Need for HTA readiness across Europe requires new approach to clinical study programs

QuintilesIMS™

Source: QuintilesIMS

Transparency initiatives are rising up and are effective in 40 Countries across Pharma, Generics and MedTech



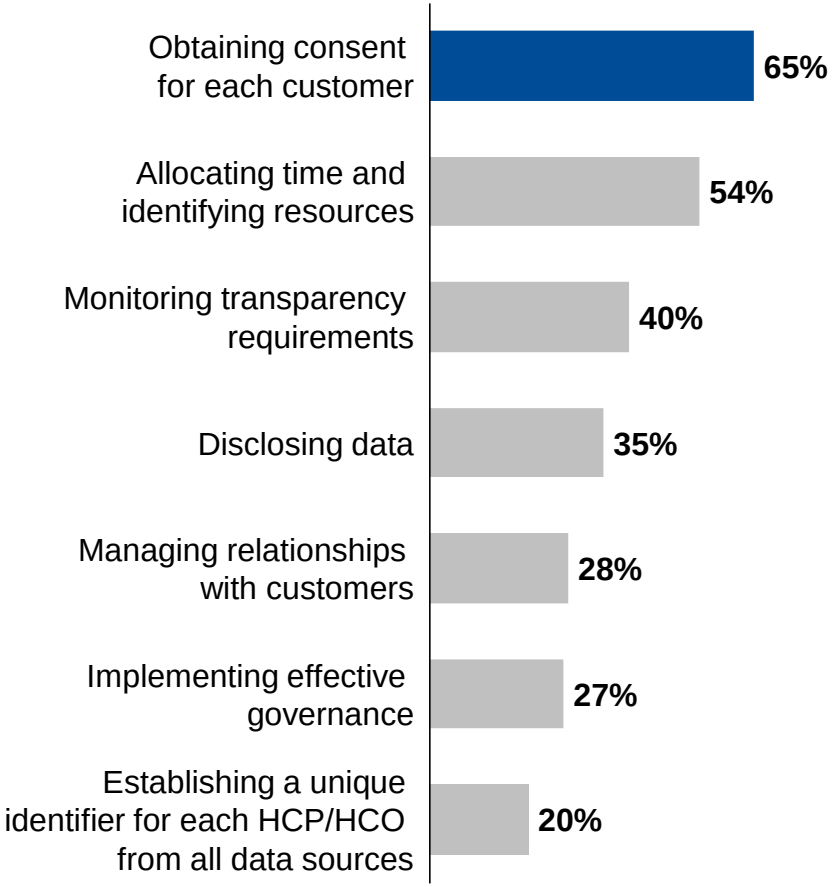
QuintilesIMS™

Source: QuintilesIMS

Obtaining consent from stakeholders is key, however status updates show that it is often missing

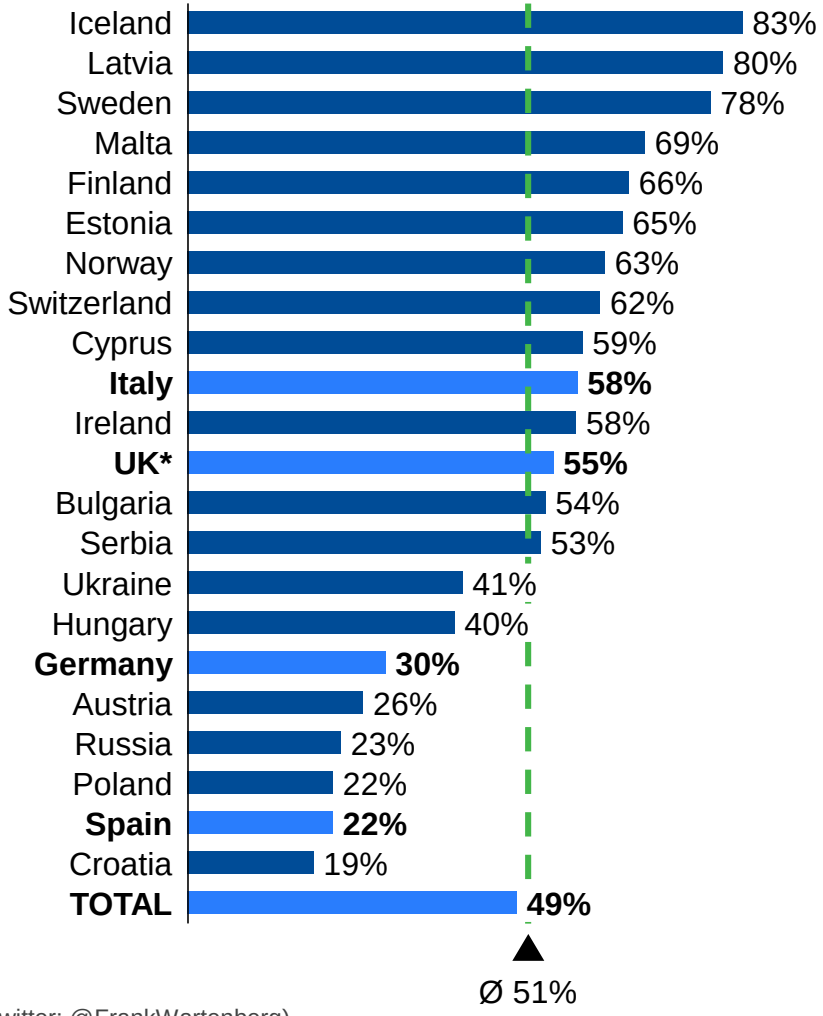
How challenging are the following process?

Percentage rating 7,8, and 9 on a 9 point scale



Consent for individual disclosure per Country

Average of Average % YES (HCP)



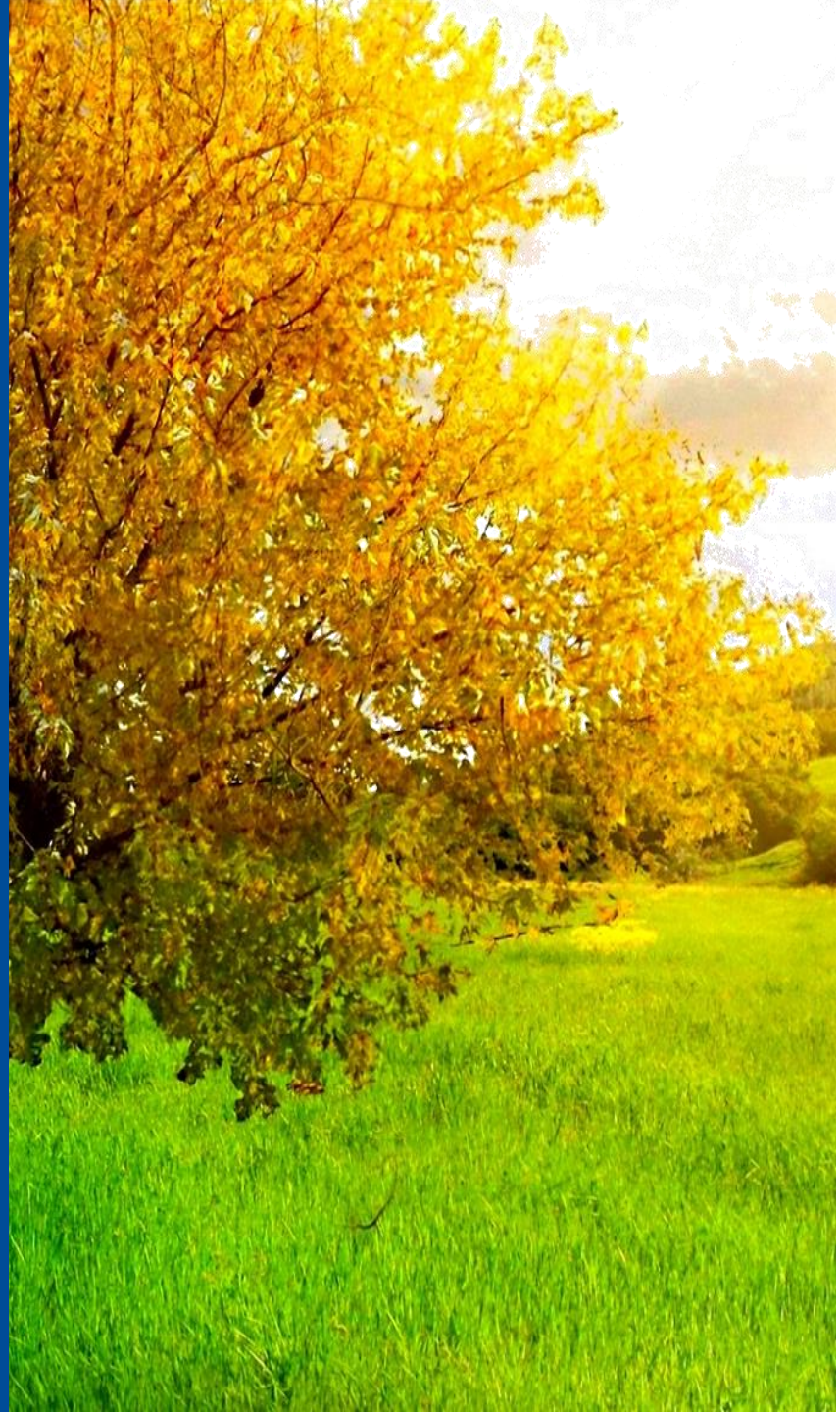
*UK estimated by ABPI at 55%
Source: QuintilesIMS

Wrap-up

1. Specialty products and TAs are the key drivers of developed market growth and challenge payer's budget
2. Biosimilars enter the market and increase competition which leads to lower prices
3. Cost pressure asks for innovative pricing models; Value assessments serve as justification for reimbursement
4. The implications of Brexit for pharma remain uncertain but will affect regulatory, trade, commercial, and scientific areas
5. Collaborative European efforts on harmonizing assessments as well as transparency regulations getting enforced

QuintilesIMS™

Source: QuintilesIMS



Thank you

Dr. Frank Wartenberg

President Central Europe

dr.frank.wartenberg@quintilesims.com

+49 69/6604-4315

Follow me on

Twitter: @FrankWartenberg

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