Challenges in the new market place

10th International Pharmaceutical Compliance Congress and Best Practices Forum

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Global growth is now on an exceptional level – forecast suggests that it will not be sustained

Developed Markets CAGR 2016-2020	
US	6%-9%
Japan	(-1)%-2%
Germany	3%-6%
UK*	4%-7%
Italy	2%-5%
France	(-2)%-1%
Spain	2%-5%
Canada	3%-6%
Developed	**4%-7%**

Pharmerging Markets CAGR 2016-20 LCUS$	
China	5%-8%
Brazil	7%-10%
India	10%-13%
Russia	6%-9%
Turkey	12%-15%
Mexico	2%-5%
Pharmerging LCUS$	**6%-9%**
Pharmerging US$	**4%-7%**

At par with region CAGR

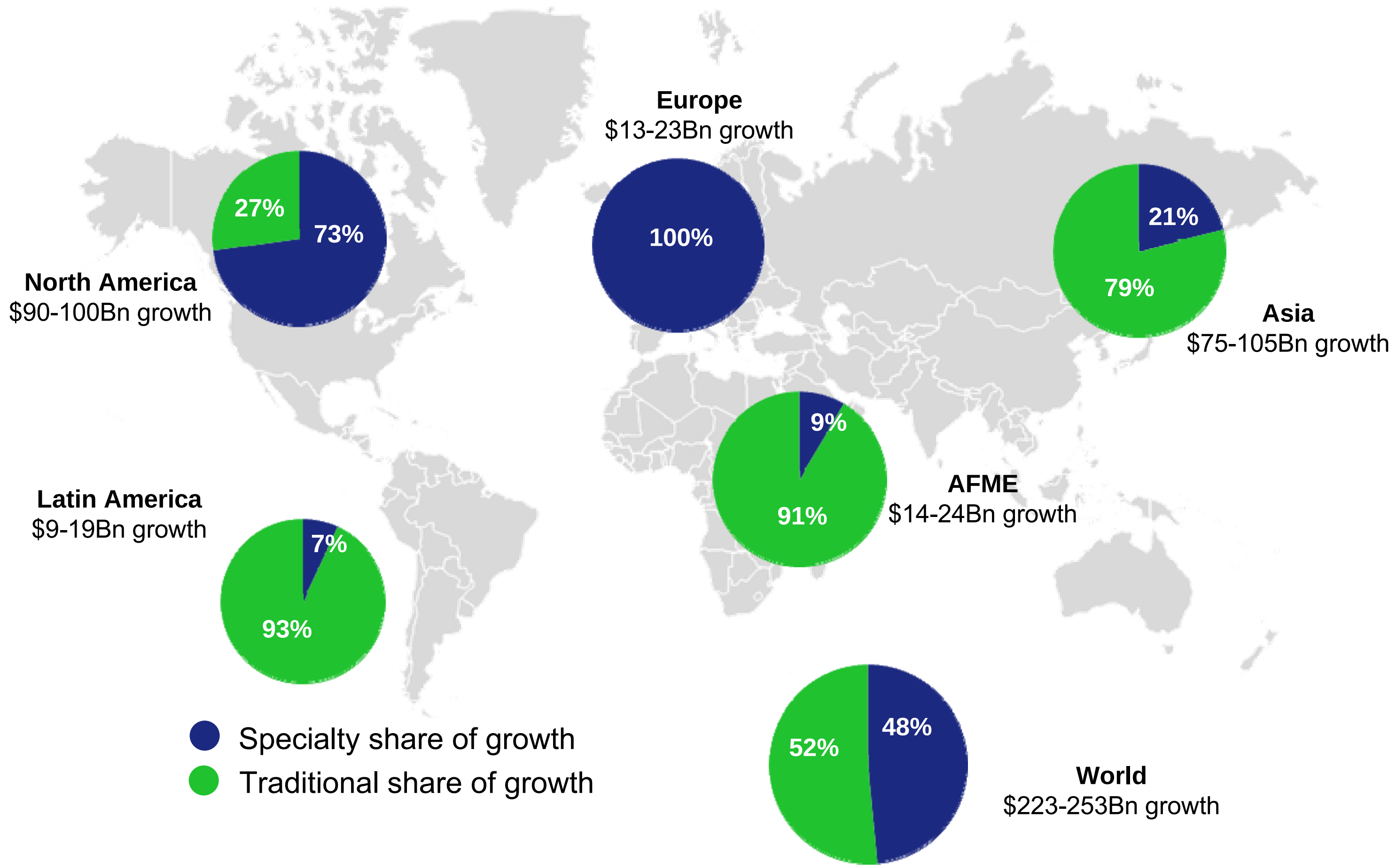
Lower than region CAGR

Higher than region CAGR

*Subject to clawback

Source: IMS Market Prognosis Oct 2015; (*) at ex-manufacturer price levels, not including rebates and discounts. Contains Audited + Unaudited data. $US used for Argentina, Venezuela, Nigeria & Ukraine due to hyperinflation

Specialty medicines drive growth in developed regions; globally, primary care dominates



Source: IMS Health Market Prognosis, April 2015; IMS Institute for Healthcare Informatics, May 2015

Europe illustrates the importance of biologic therapies

Top 10 Products in Europe 2010-2015

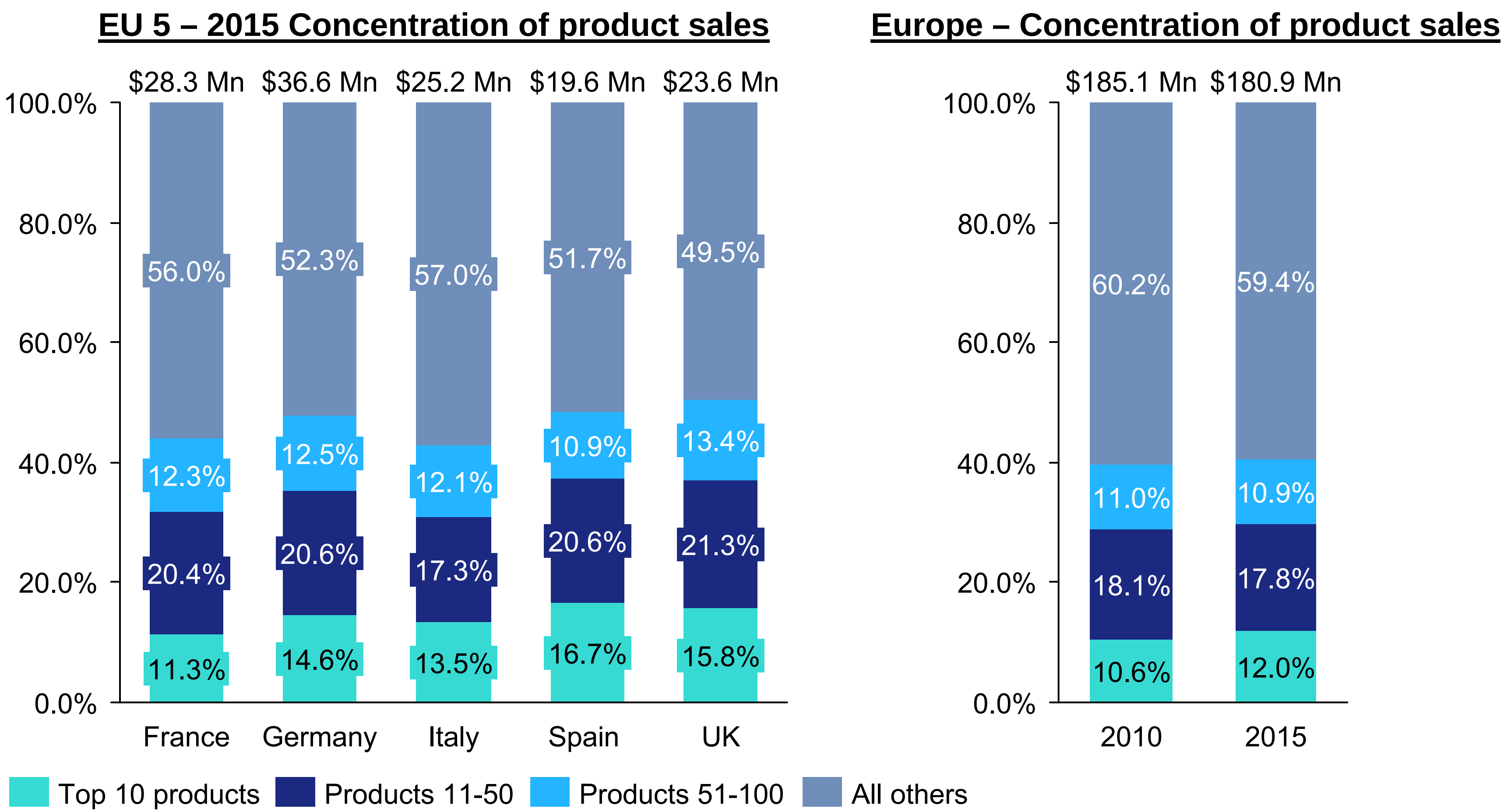
	2010	2011	2012	2013	2014	2015
1	LIPITOR	HUMIRA	HUMIRA	HUMIRA	HUMIRA	HUMIRA
2	SERETIDE	SERETIDE	SERETIDE	ENBREL	ENBREL	HARVONI
3	HUMIRA	LIPITOR	ENBREL	SERETIDE	HERCEPTIN	SOVALDI
4	ENBREL	ENBREL	HERCEPTIN	HERCEPTIN	SERETIDE	ENBREL
5	HERCEPTIN	HERCEPTIN	MABTHERA	REMICADE	REMICADE	HERCEPTIN
6	AVASTIN	LOVENOX	REMICADE	MABTHERA	MABTHERA	AVASTIN
7	LOVENOX	MABTHERA	LOVENOX	AVASTIN	AVASTIN	MABTHERA
8	MABTHERA	REMICADE	AVASTIN	LOVENOX	LYRICA	REMICADE
9	ZYPREXA	AVASTIN	SPIRIVA	LUCENTIS	LOVENOX	LOVENOX
10	REMICADE	SYMBICORT	LYRICA	LYRICA	SOVALDI	SERETIDE
No. Biologics in Top 10	7	7	7	8	7	7

Small molecule   Biologica   Small molecule specialty product

Source: IMS Health, MIDAS, MAT Q4 2015 . Rx only. Europe excludes Russia and Turkey

There is a high concentration of spending to Top 50 products across Europe

EU5



Source: IMS Health, MIDAS Restricted, MAT Q4 2010-Q4 2015 . Rx only. Europe excludes Russia and Turkey

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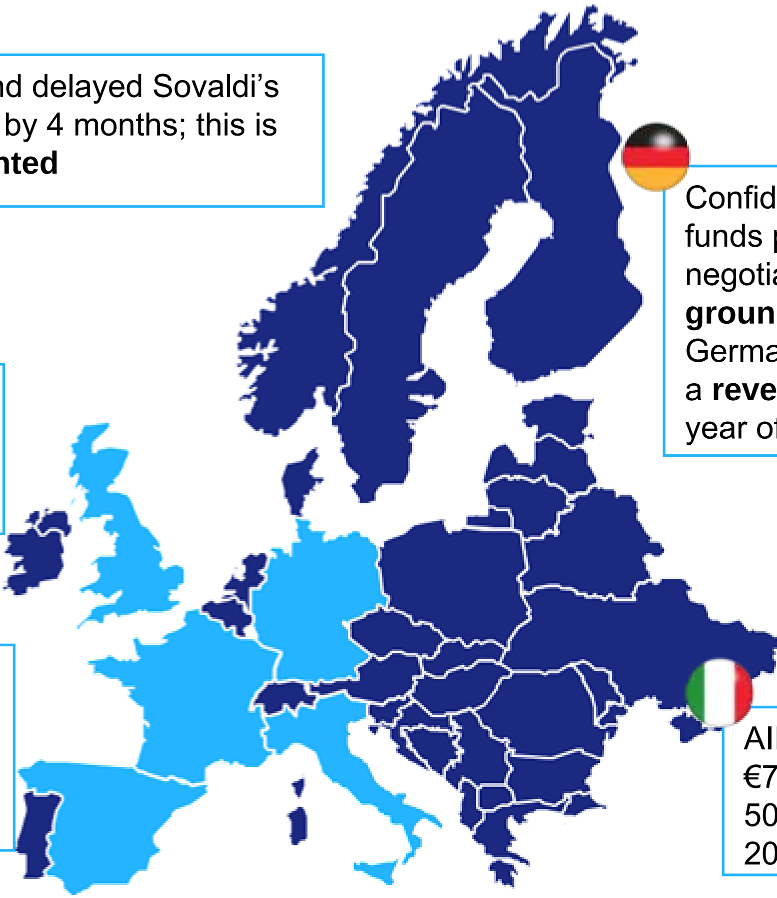
High-cost products like Sovaldi influence decision-makers in their reimbursement strategy

EU5



NHS England delayed Sovaldi's introduction by 4 months; this is **unprecedented**

Confidential discount with some sick funds prior to the GKV-SpV negotiation oucome, which is **ground-breaking**
German government attempts to set a **revenue threshold** for the first year of free-pricing at €250m

Agreement to refund the cost of Sovaldi for any patient not cured; this type of agreement is **not common** in France

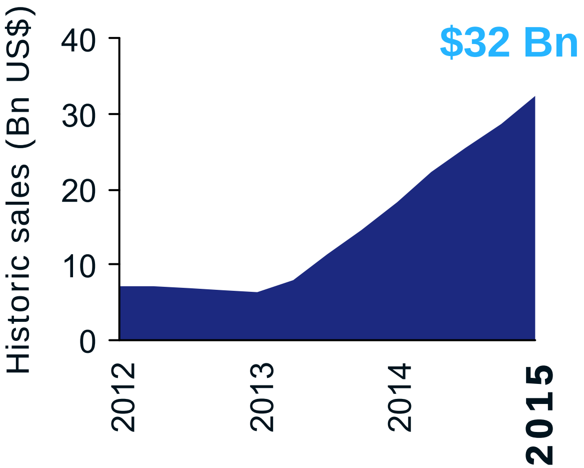
MSSSI set population maximum expenditure caps for each recent innovative HCV launch separately (€125m/year for Sovaldi)

AIFA set up an ad hoc fund of €750m to treat a maximum of 50.000 patients with Sovaldi in 2015

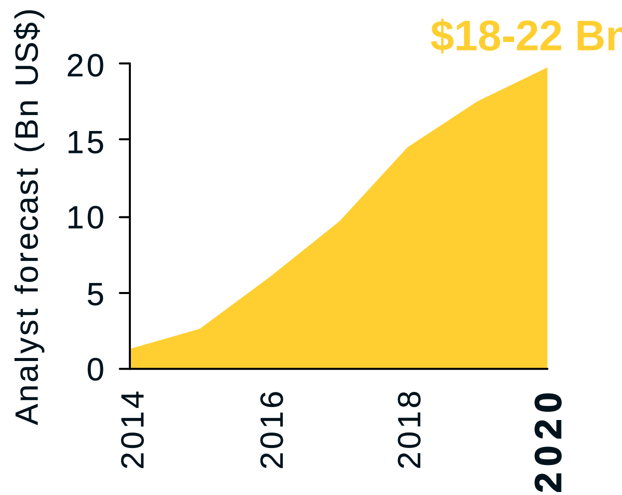
Sovaldi only the first of several potential tsunamis

Are these innovations sustainable?

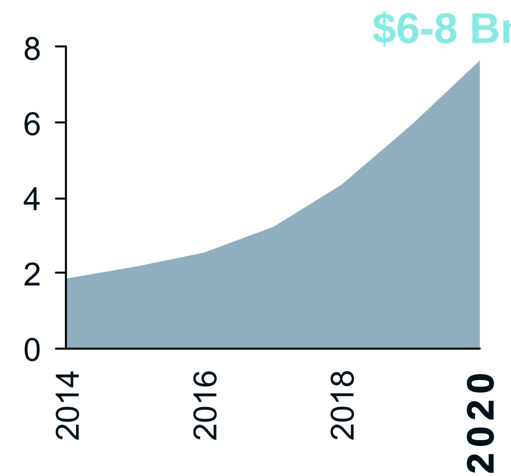
Hepatitis-C market
2012-2015



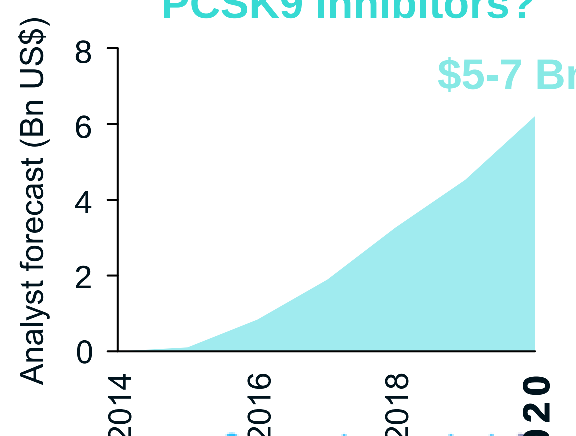
Immuno-Oncology



Respiratory biologics



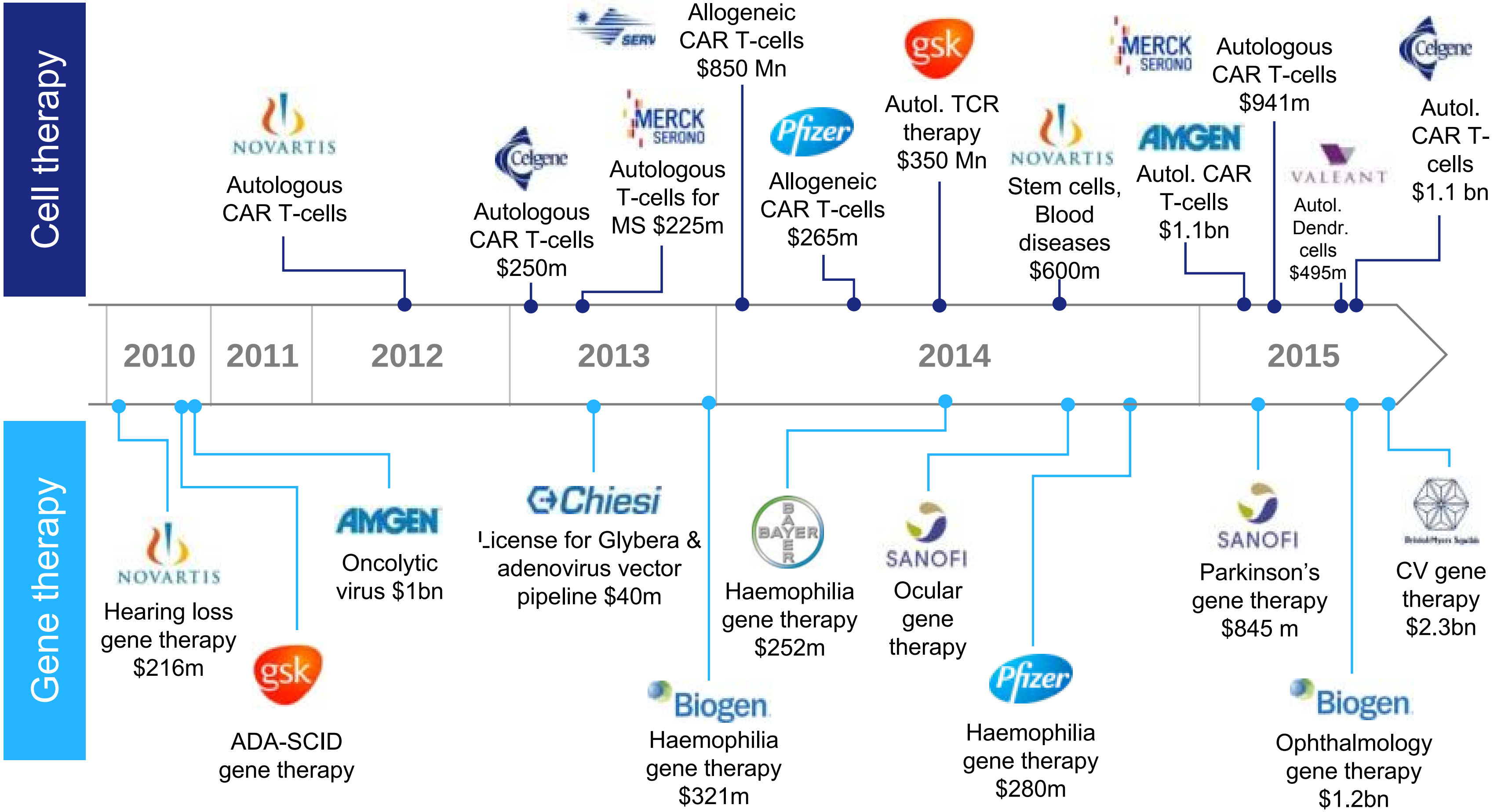
PCSK9 inhibitors?



Source: IMS Health Analytics Link consensus analyst forecast; Drug analyst consensus; IMS Health MIDAS Q4 2015;

… and Cell & Gene Therapies are arriving soon

Cell & Gene Therapy – Major companies are now actively engaged

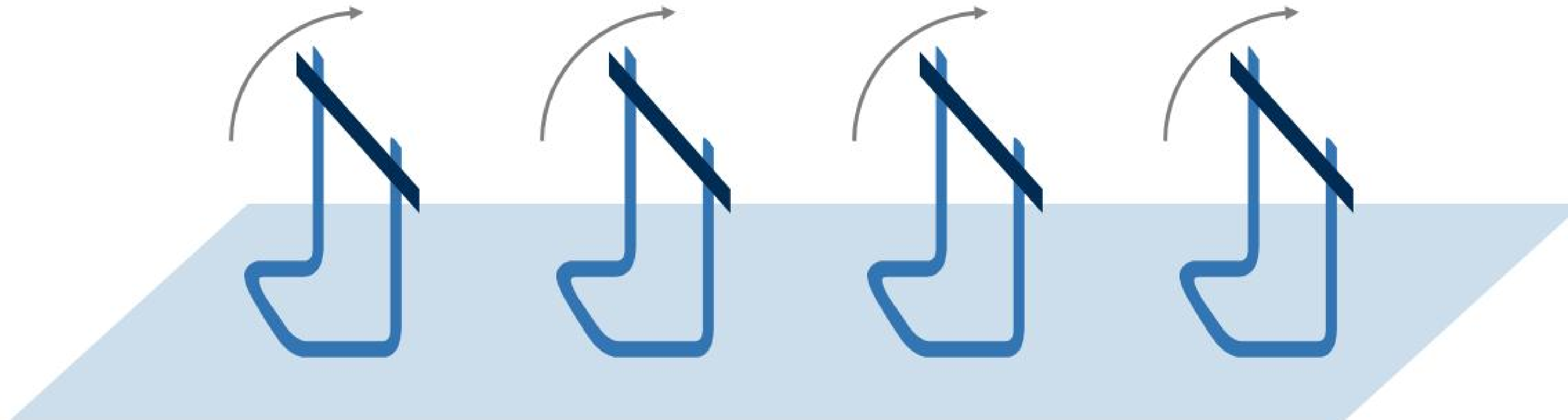


Source: IMS Health Thought Leadership analysis March 2015; IMS Health Pharma Deals; deal values incl. milestones

A restricted funding environment challenges Pharma to demonstrate value

Payer Interventions

Clinical Evidence; Reimbursement Assessment	Pure cost containment	Reallocating resources to value	Sustained evidence of value to payer



Clinical evidence stricter at both regulatory and national reimbursement levels: Payers demand H2H comparisons, addressing unmet need	Payers' increasing cost containment measures to balance and prioritise budget spend	Tangible and measurable incremental benefit Addresses healthcare priorities	Pharma increasingly having to find common ground to <u>achieve or sustain access</u>

Challenges in Europe are numerous and uncertain

PMA uncertainty

Price negotiation collaboration

- NL and BE announced pilot joint price negotiations for orphan drugs
- GR and PT health ministers call for increasing payer collaborations
- Increased transparency of net price

payers' insights

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 Cancer Drugs Fund being taken in under NICE QALY assessment
- NICE QALY threshold being reviewed
- French and Italian MoH reviewing current drug reimbursement system

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
SCIENCE MEDICINES HEALTH

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

Joint Action 1 (2010-2012)

- 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

Joint Action 2 (2013-2015)

- 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)

Coordinator: Danish Health Authority

Joint Action 3 2016 - 2019

- 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.

Coordinator: Zorginstituut Nederland (ZIN)

Source: EUnetHTA website

Question is… is value defined in the same way?

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* (green)

Negative unanimous agreement* (red)

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

Source: HTA body websites

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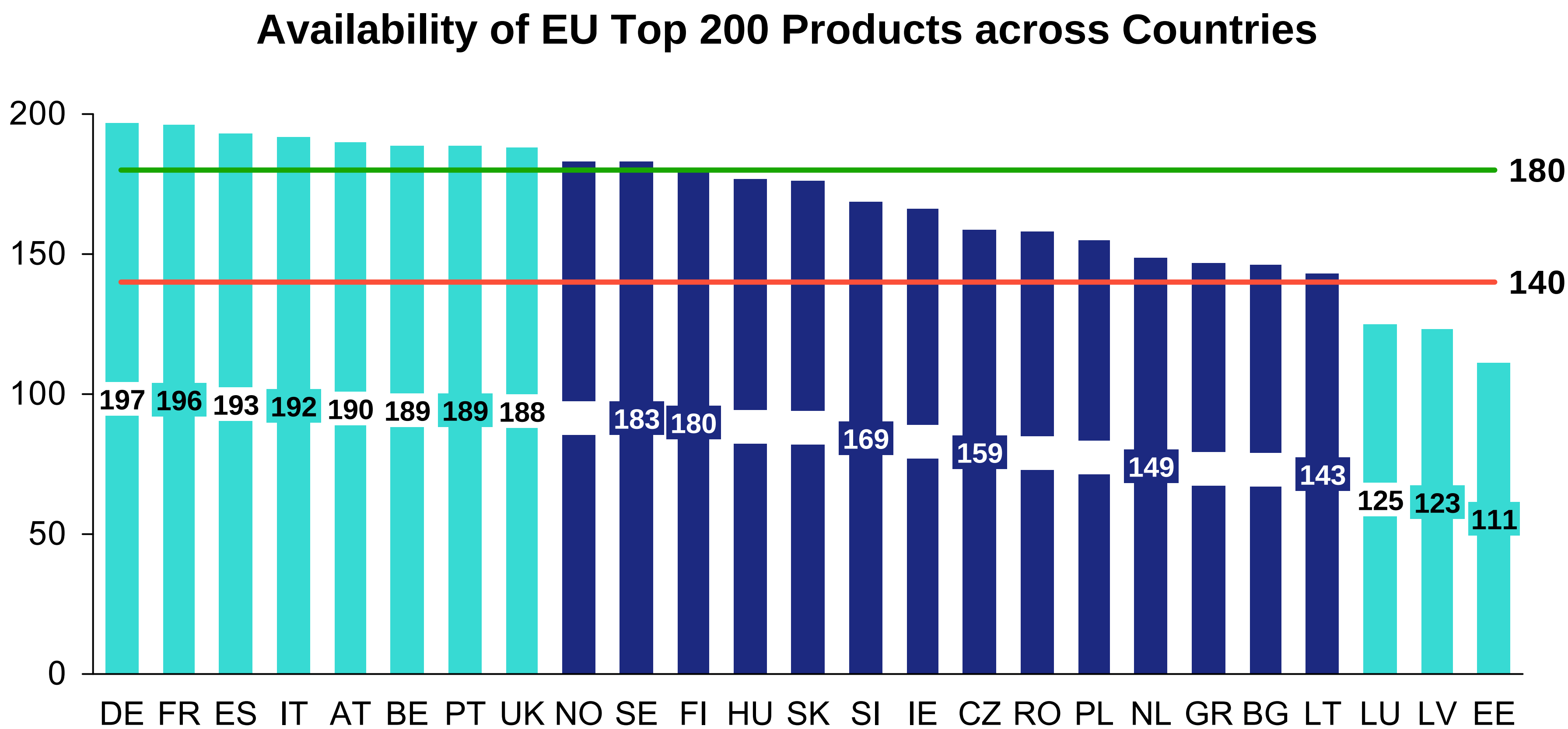
In most EU countries only ~70-90% of the top 200 selling products are available in the market

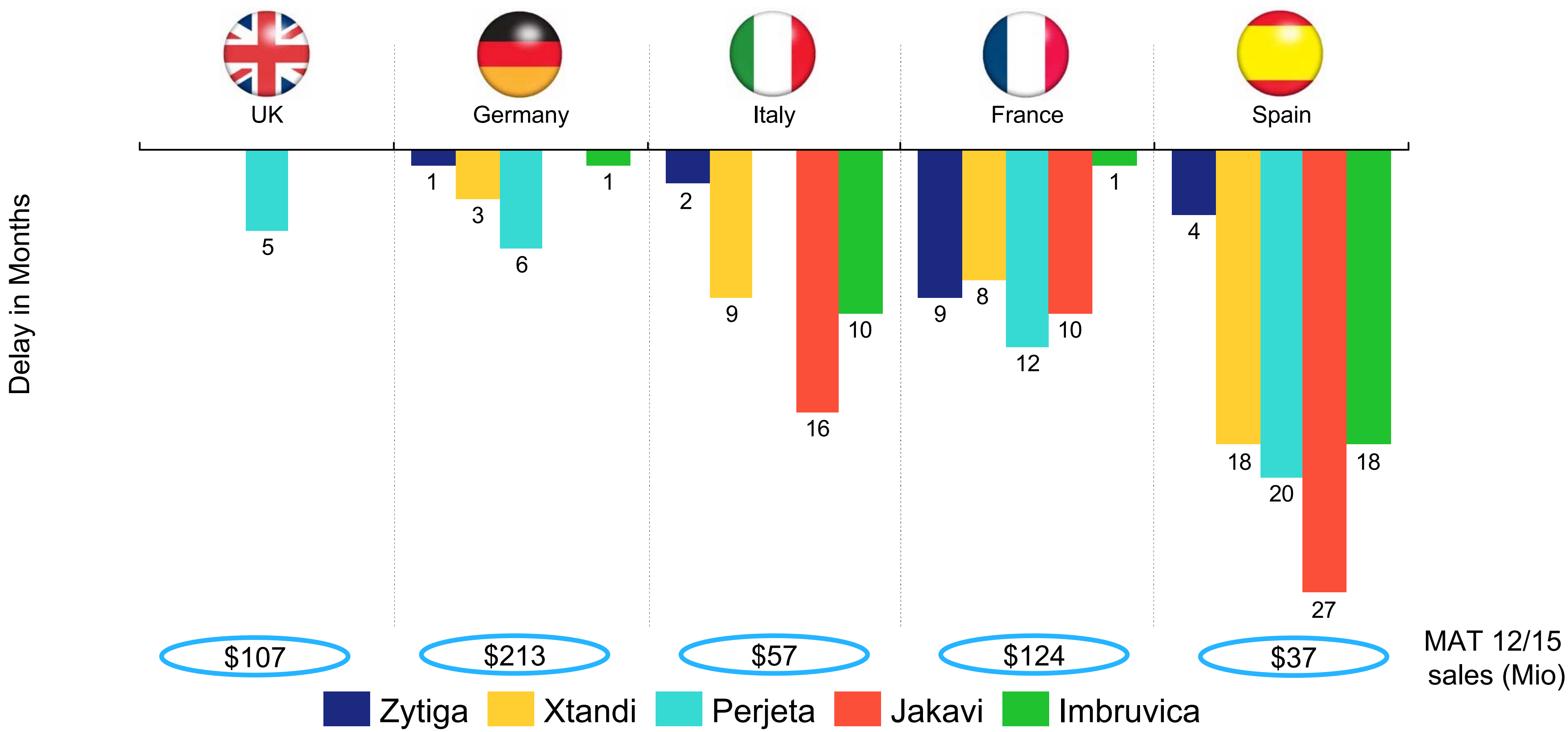


Source: IMS Health MIDAS. 2015.

Launch rollouts of innovations across EU5 diverge greatly: Germany is key

EU5

Top 5 onco drugs (launched 2011-2015), delay from 1st country's launch, EU5



Source: IMS Health, MIDAS December 2015, 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.
Imbruvica not launched yet in Spain (the 18 months equal the time between first launch and April '16)

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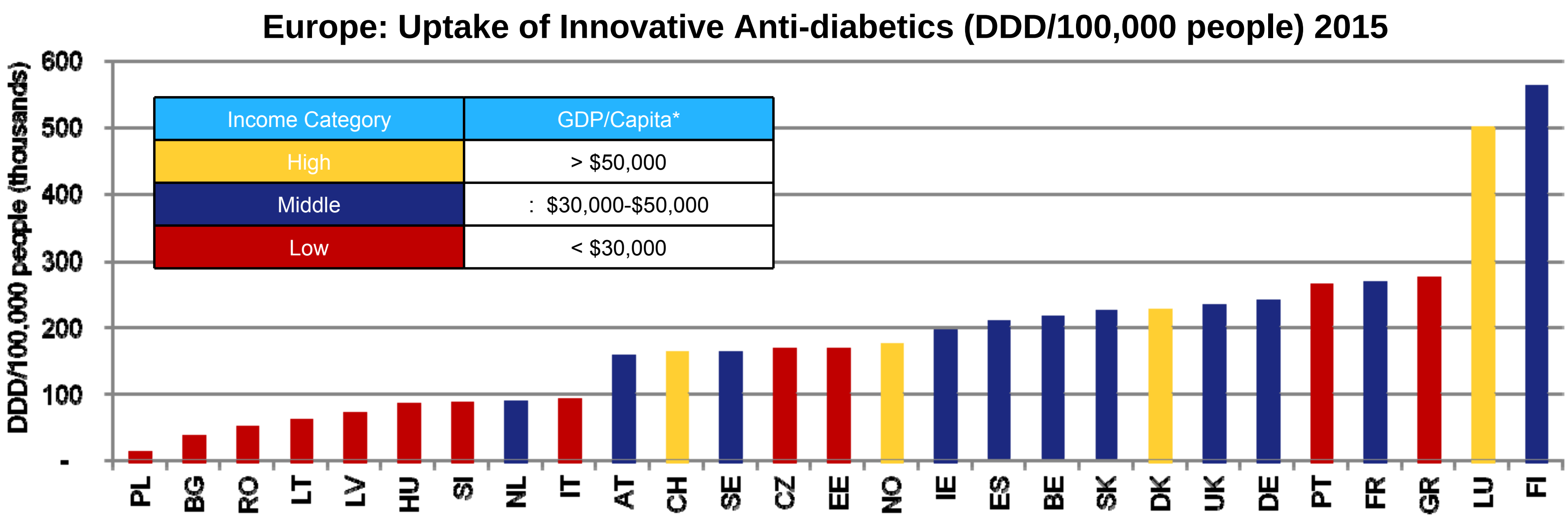
Looking at innovative anti-diabetics shows very large country differences in uptakes



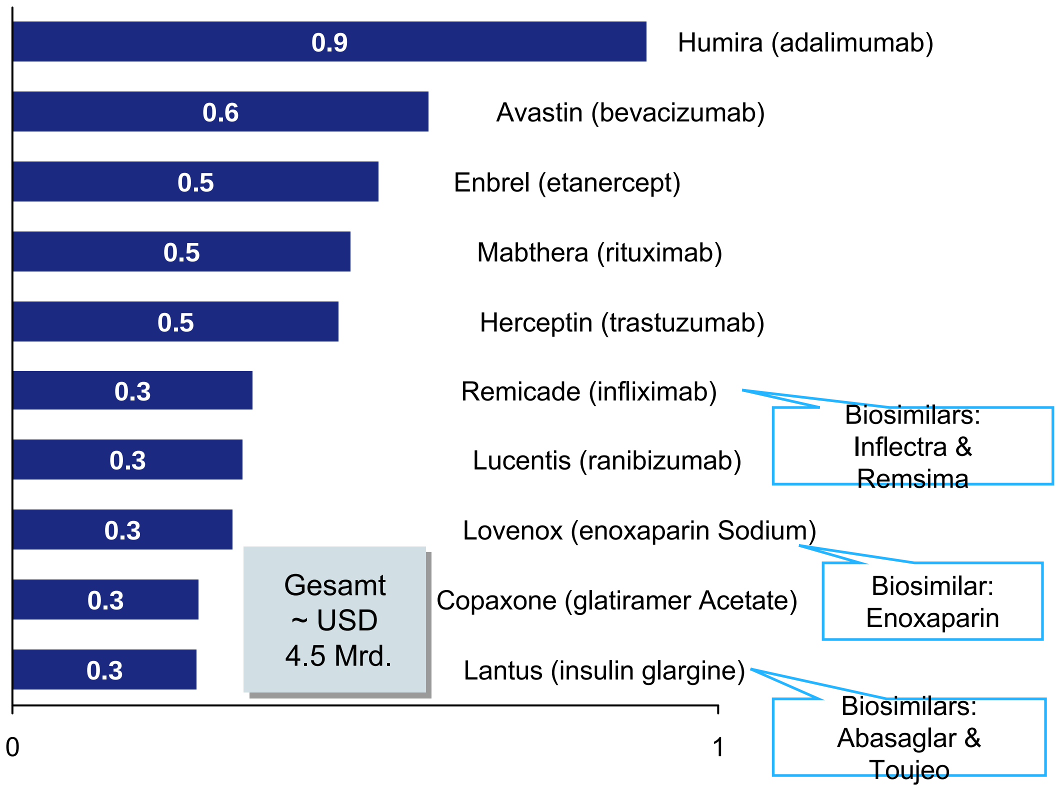
Many factors can affect uptake :

- 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

Source: IMS Health MIDAS 2015. Population figures from Eurostat. * OECD health accounts data. June 2012

Important biologics already lost or are about to lose exclusivity in the near future

Top 10 Biologics 2015, Sales Billion (USD)

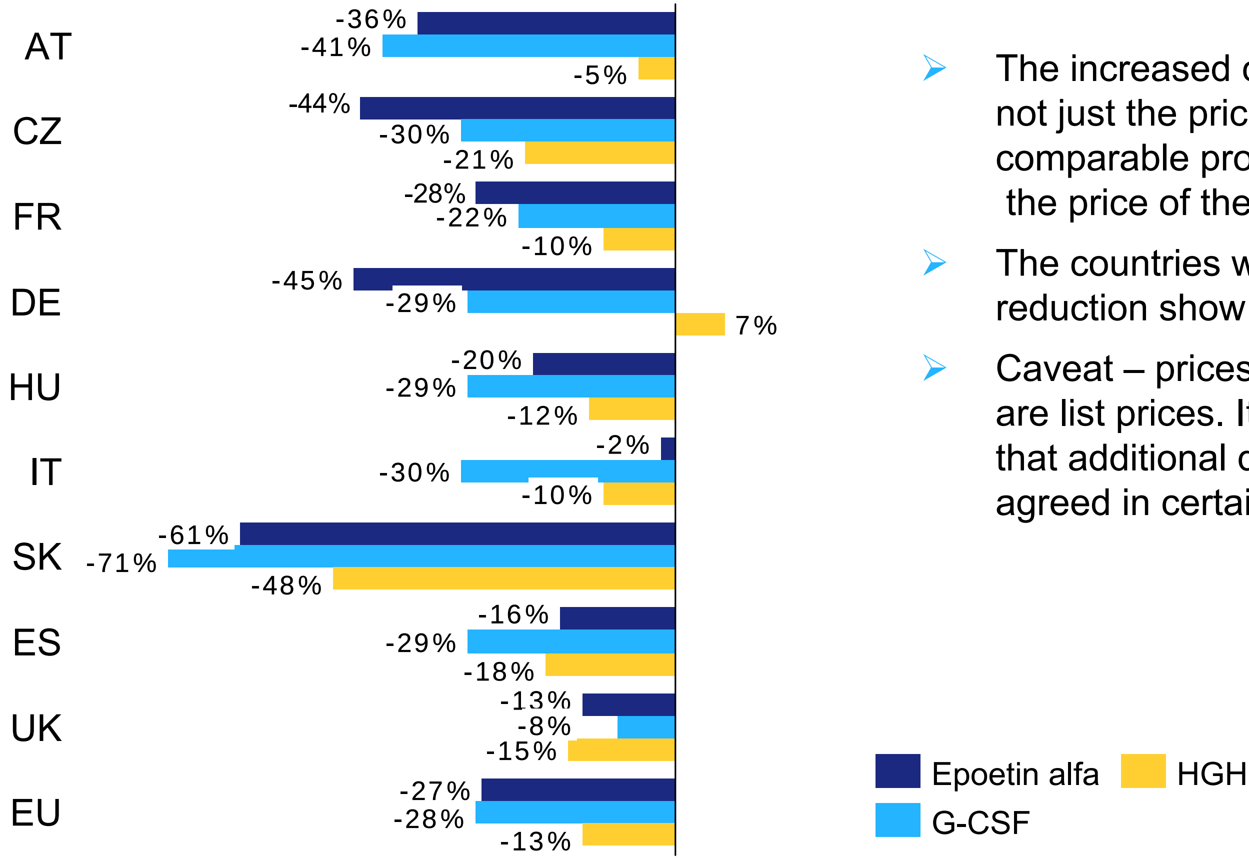


EU Patent expiry date	US Patent expiry date
2018	2016
2019	2019
Expired	2028 (postponed)
Expired	2018
Expired	2019
Expired	2018
2016	2016
Expired	Expired
2017	Expired
Expired	Expired

Source: IMS MIDAS, Q4 2015, only Rx, IMS Health analysis

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

Price per treatment day (2014/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 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 (2015): The Impact of Biosimilar Competition

In less than 2 months, the first disclosure for EFPIA will take place

EFPIA HCP/HCO Disclosure Code
June 24th 2013

EFPIA Code of Practice

Data collection by member companies
from January 2015

Publication
until: June 30th 2016

2013 | **2014** | **2015**

- **Aggregate R&D**
- **Healthcare-Organizations**
- **HCPs**

Disclosure in 2016 based on 2015 data

efpia

Source: IMS Health 2014 European Trends in Aggregate Spend, Transparency & Disclosure

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

Consent Status from EFPIA members

- **Poland – Infarma**
  – January 2015 - 12% Consent
  – December 2015 – 23% Consent
- **Germany- Vfa/EFPIA**
  – April 2015 – 50-55 % Consent
  – October 2015 - 40-45% Consent
- **UK – ABPI Survey**
  – 2015 – 69 % Consent
- **Spain – Farmaindustria**
  – April 2015 – Approx. 10% Consent
  – October 2015 – Approx. 25% Consent

Consent Status from IMS Health Consent solutions users

- **Spain**
  – October 2015 3% Consent
  – February 2016 2,2 % Consent
- **Germany**
  – October 2015 57% Consent
  – February 2016 27% Consent

Source: IMS Health: 2015 European Aggregate Spend, Transparency and Disclosure, 2016 EUROPEAN USER GROUP MEETING

Wrap-up

1. Growth in the pharmaceutical market mainly comes from specialty care
2. Uptake and launch roll-out differs between EU countries
3. Value assessments serve as justification for pricing/reimbursement, however high-cost products are subject to further cost containments
4. Biosimilars enter the market and increase competition which leads to lower prices
5. European Transparency Initiative affects all pharmaceutical companies – biggest challenge in obtaining consent from stakeholders

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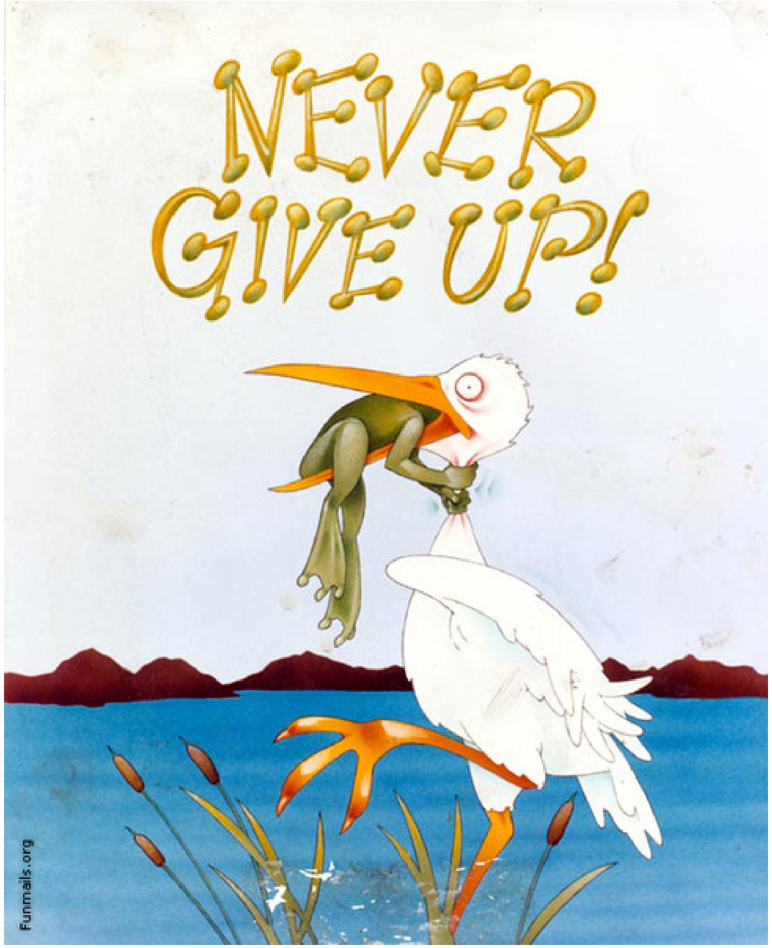

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