Disruption and maturity: the next evolution of biologics

Sarah Rickwood, Vice President, Thought Leadership

Four facts about the biologics market

1. Continued growth, but increasing maturity

2. Huge clinical potential

3. Exciting science

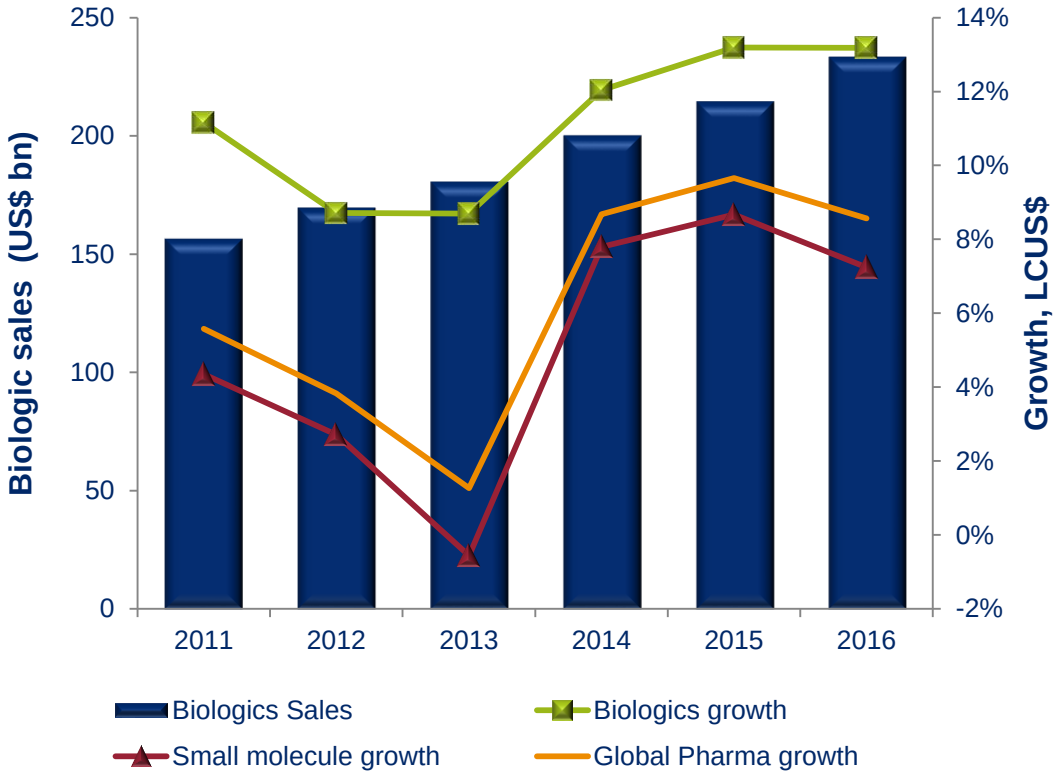
4. An immature market

Biologics has trended consistently above the growth of the global market, in good times and band

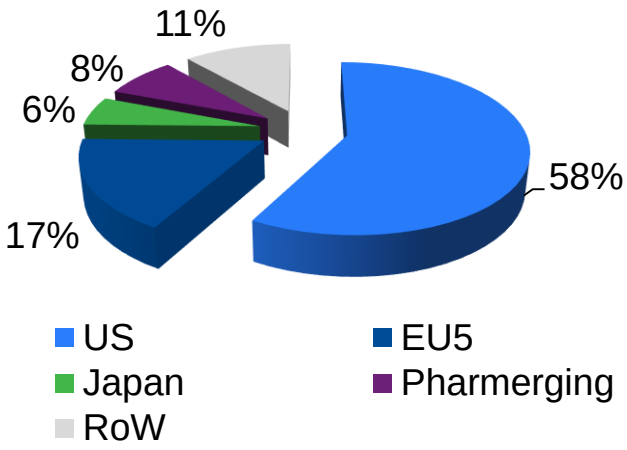
The US is overwhelmingly the most important market

Global biologic sales and trends

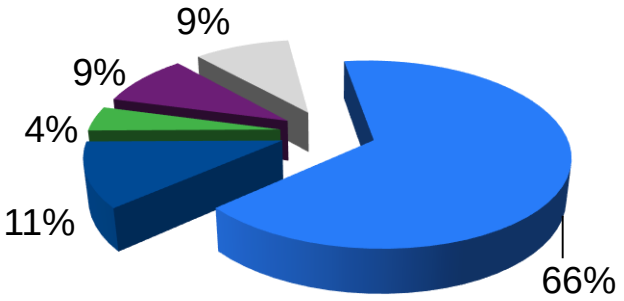
2011-16



Biologics – 2016 Share of sales



Biologics – Share of 5 yr growth



Source: QuintilesIMS MIDAS MAT Q2 2016; Share of growth in LC$. Brazil and Mexico non-retail included

As the largest biologics market, the US is also leading maturation

Biologics: Highly competitive indications and targets

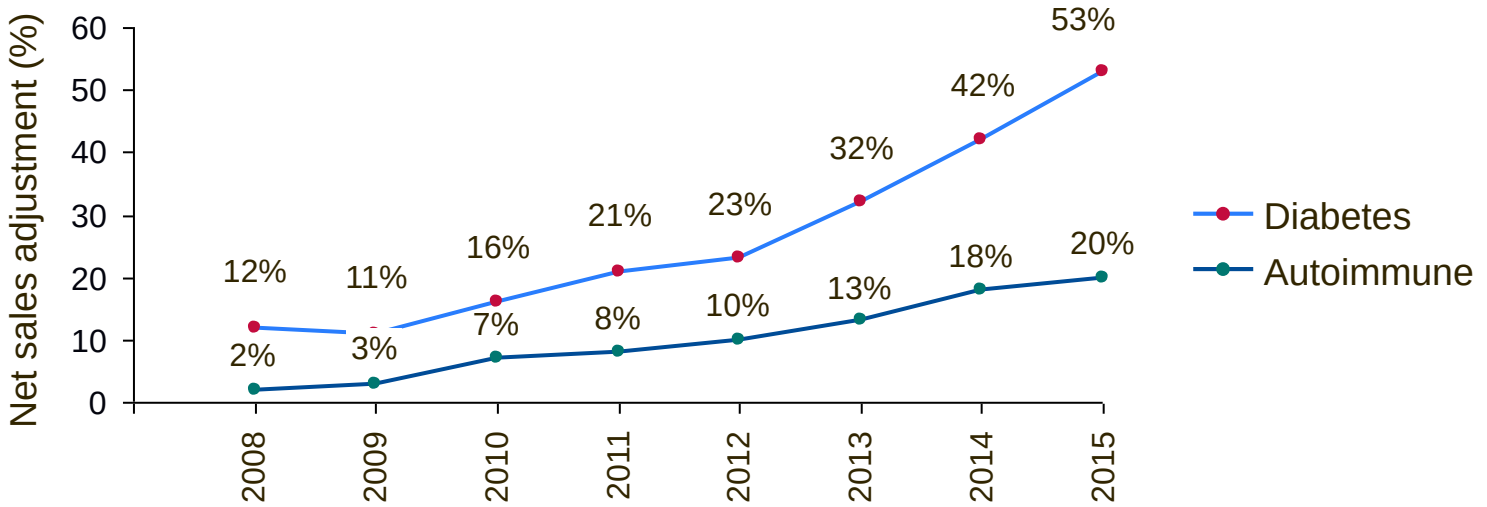
- Autoimmune: (RA, Psoriasis)
- Diabetes: (LA Insulin, SA Insulin, GLP-1)
- Oncology: (Checkpoint inhibitors, EGFR)
- Respiratory: (IL5, IL-13)
- Dyslipidaemia: (PCSK9)

Several biologic molecules with the same MoA. Me-too's?

Some typical biologic TAs are seeing small molecules competition

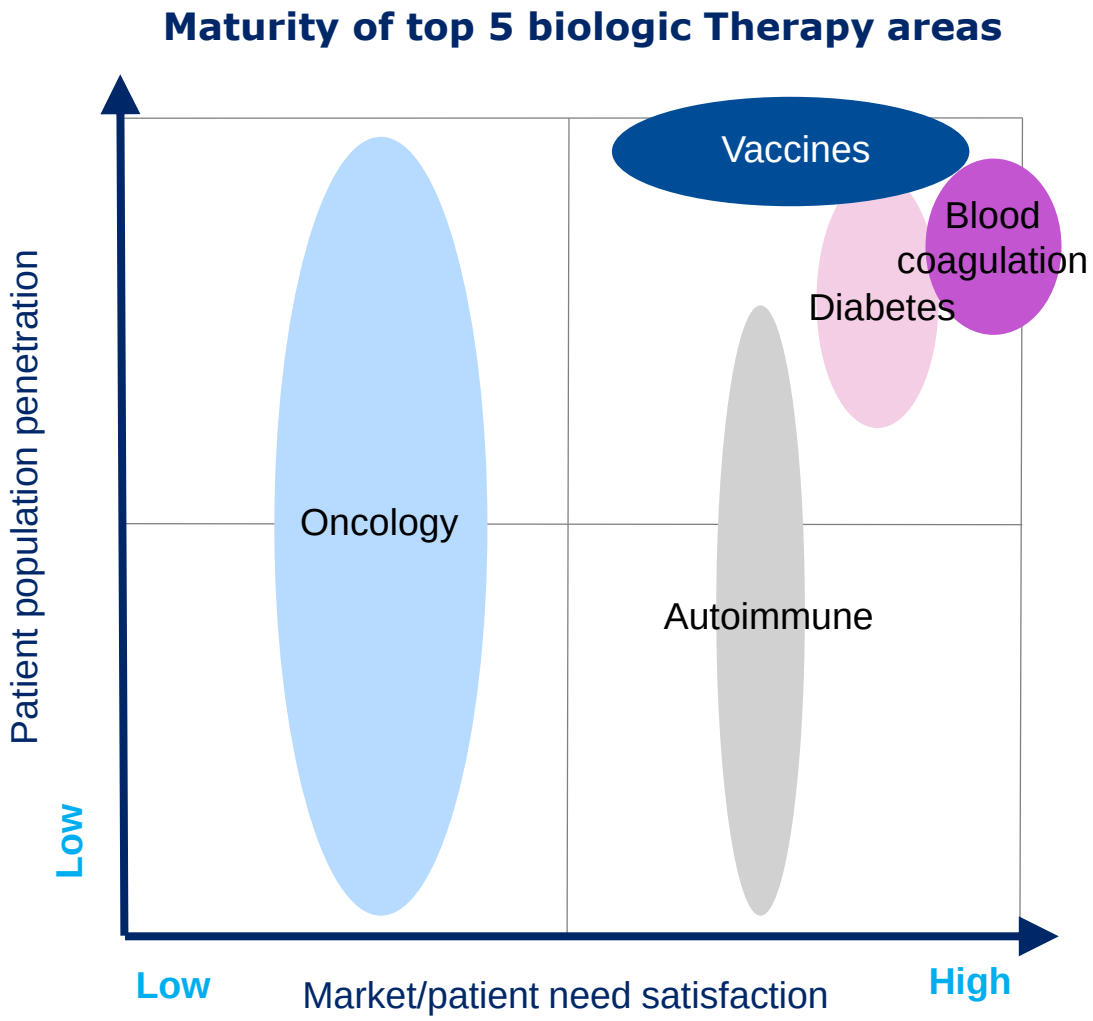
Higher promotional spending requirements

US: Diabetes and Autoimmune Net sales adjustment *

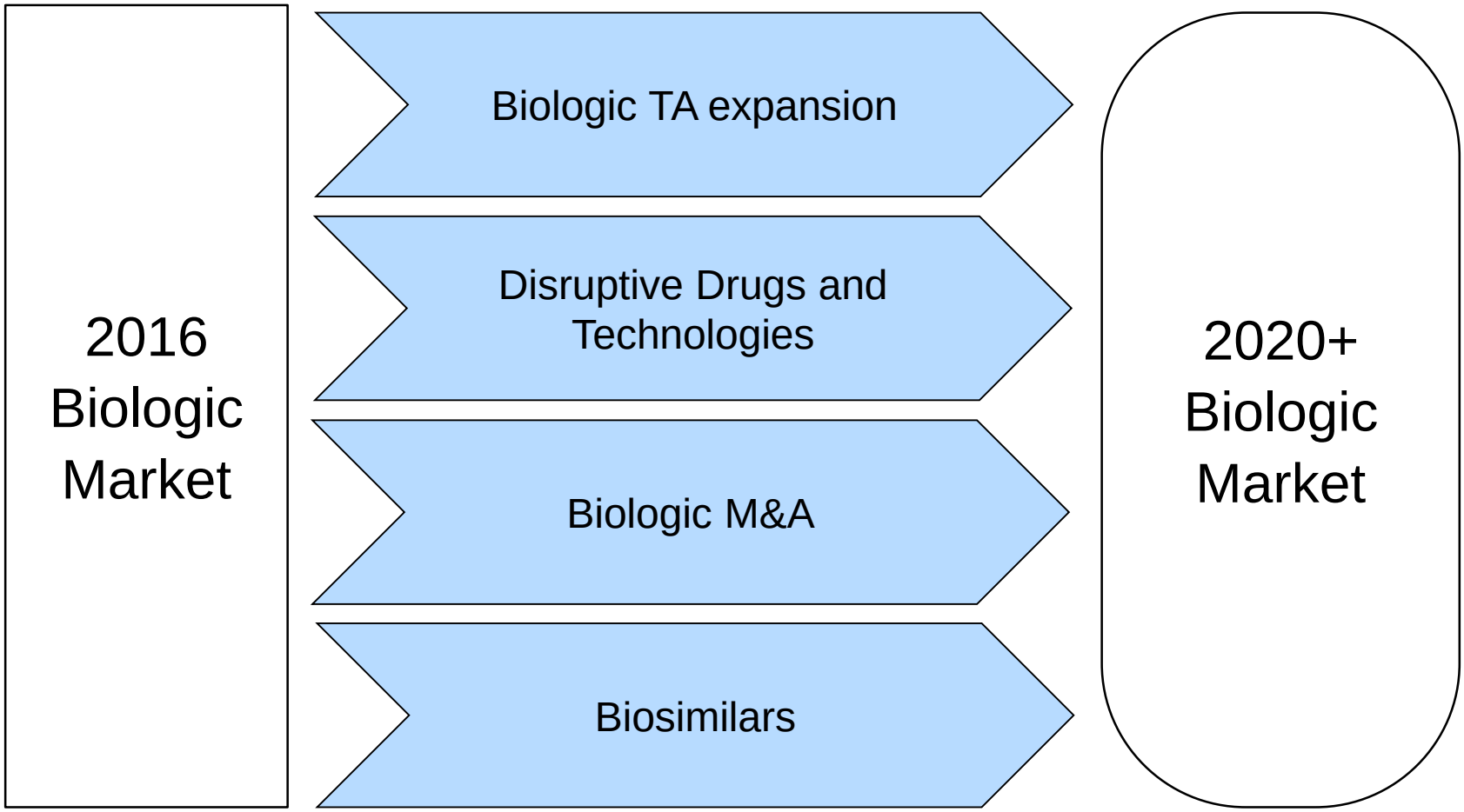


Source: IMS Institute for Healthcare Informatics, MIDAS Dec 2015, annual company reports; *Diabetes and Autoimmune definition includes biologics and biosimilars

Several therapy of the biologic market have now reached maturity – we are in a new era



Four trends to create the biologics market beyond 2020



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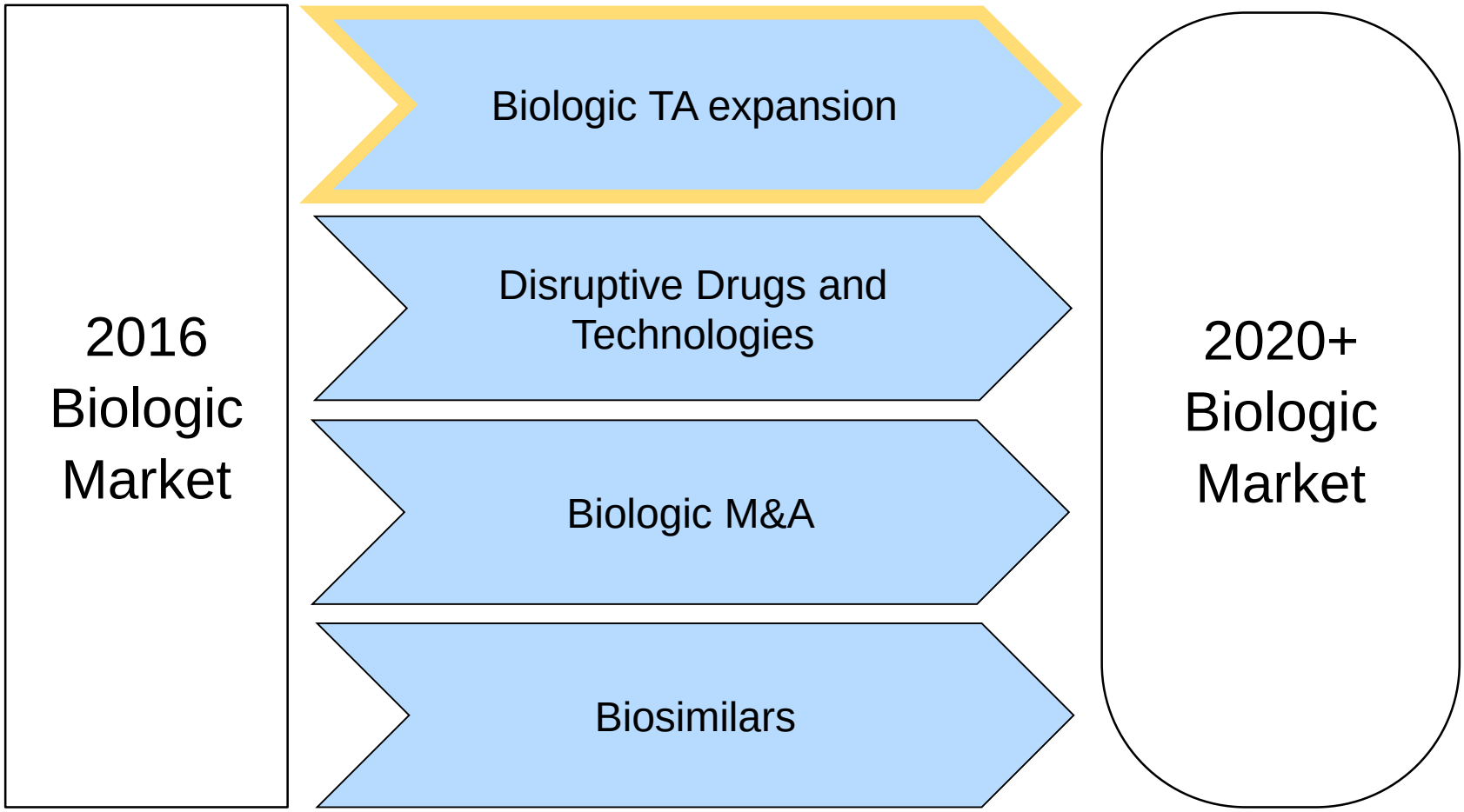
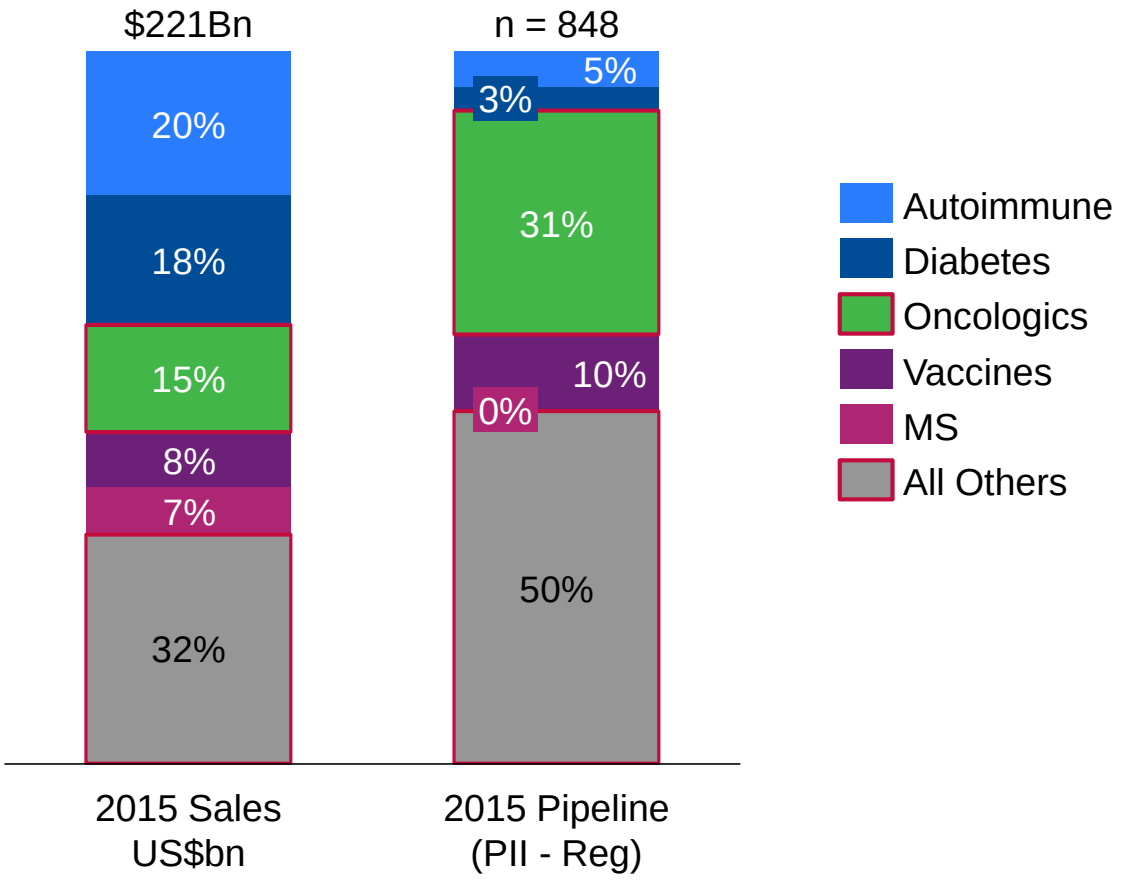


Oncology will be increasingly dominant, but new TAs for biologics proliferate

Half of the biologic pipeline falls outside of the top 5 biologic TAs

Biologic sales and PII+ pipeline by Therapy Area 2015

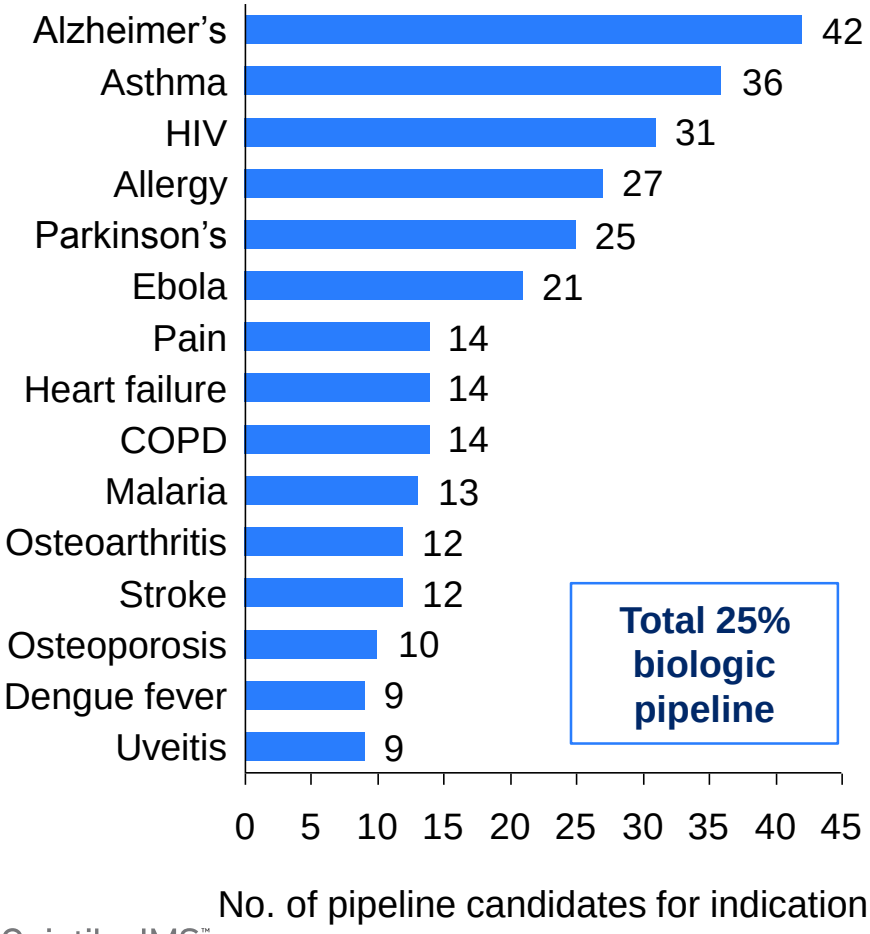


Source: QuintilesIMS MIDAS MAT Q4 2015

Over the next five years biologics will enter indications not typically treated with biologics

Biologic pipeline: non-traditional biologic indications

(Pre-Clin to Reg)



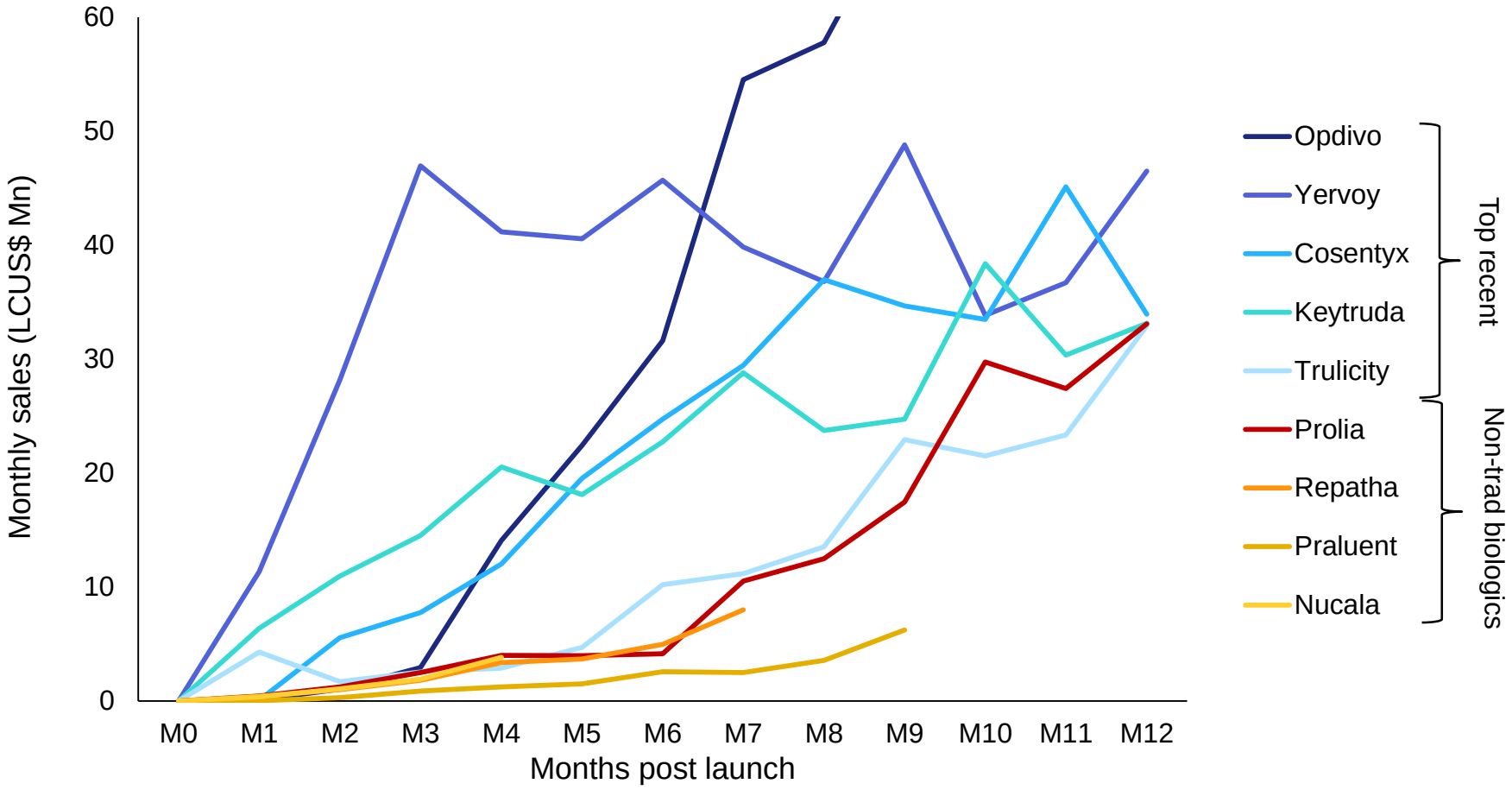
Common Factors

- Dominated by small molecules – highly genericised
- High patient population
- Aim to treat severe subsections of these indications
- High cost per patient cause payer concern
- Mixed experience to date with pioneer biologics taking this route (Xolair in respiratory, Praluent in hyperlipidemia)
- Biologic specific challenges such as patient targeting, infrastructure and administration

Source: QuintilesIMS R&D Focus Q4 2015; Thought Leadership analysis

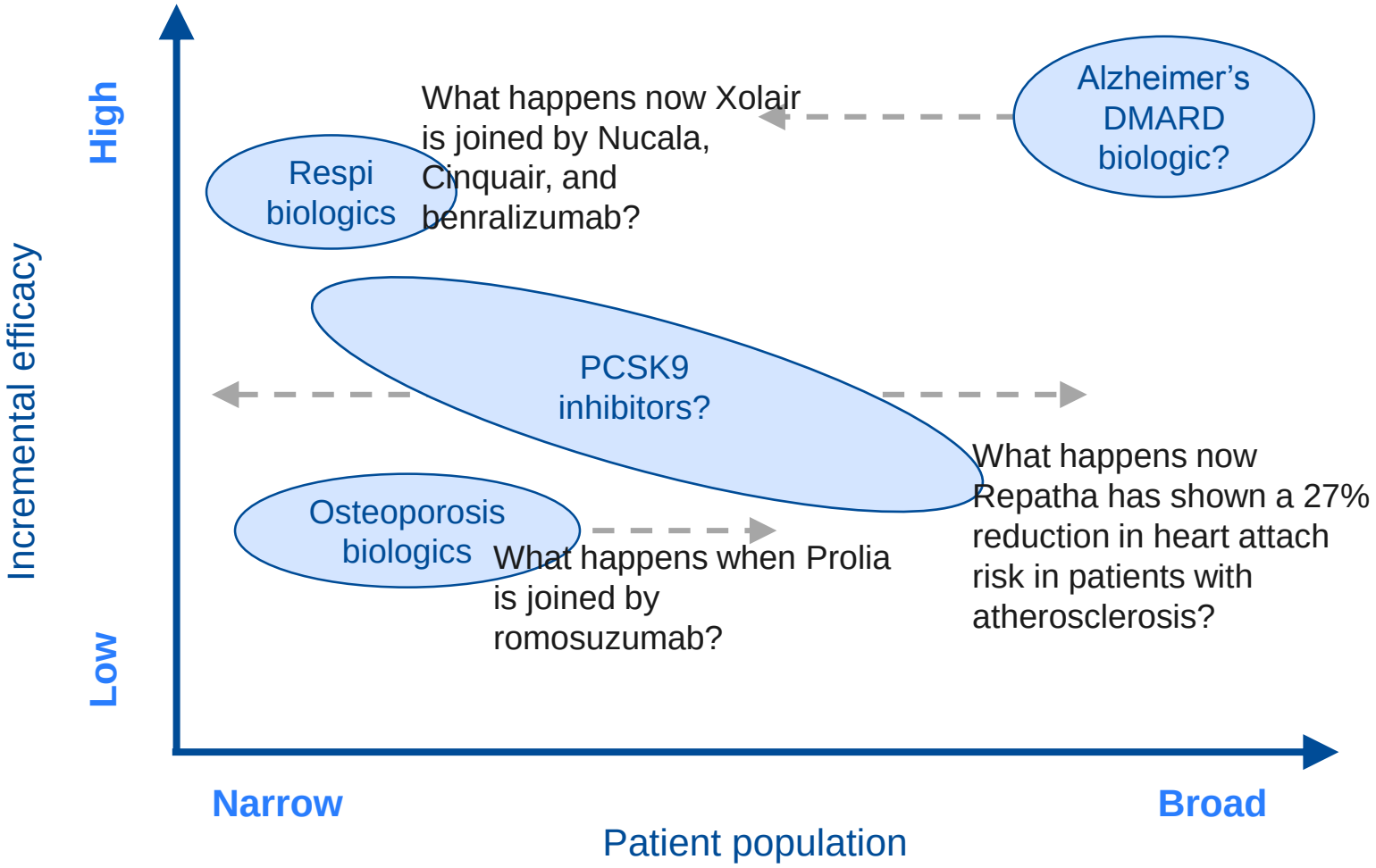
However, there remains a sales challenge for the biologics entering non traditional areas

US launch: Top recent biologic launches vs. biologics in non-traditional therapy areas



Source: IMS Health MIDAS Q4 2015; Top recent launches are top launches within the last 5 years

New biologics will see profound change in the next five years..



Souce: QuintilesIMS The next frontier for biologics: Non-traditional Therapy Areas

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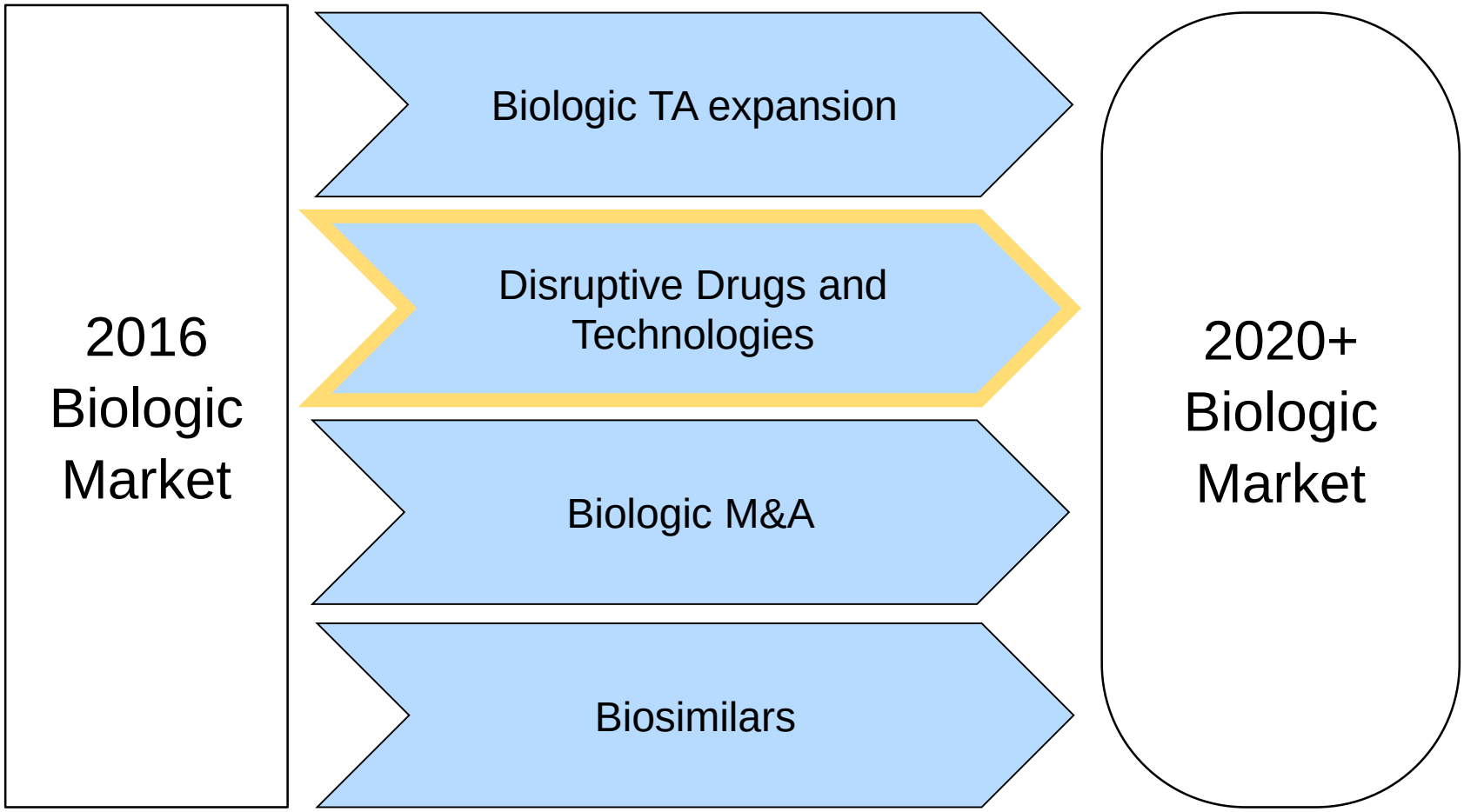
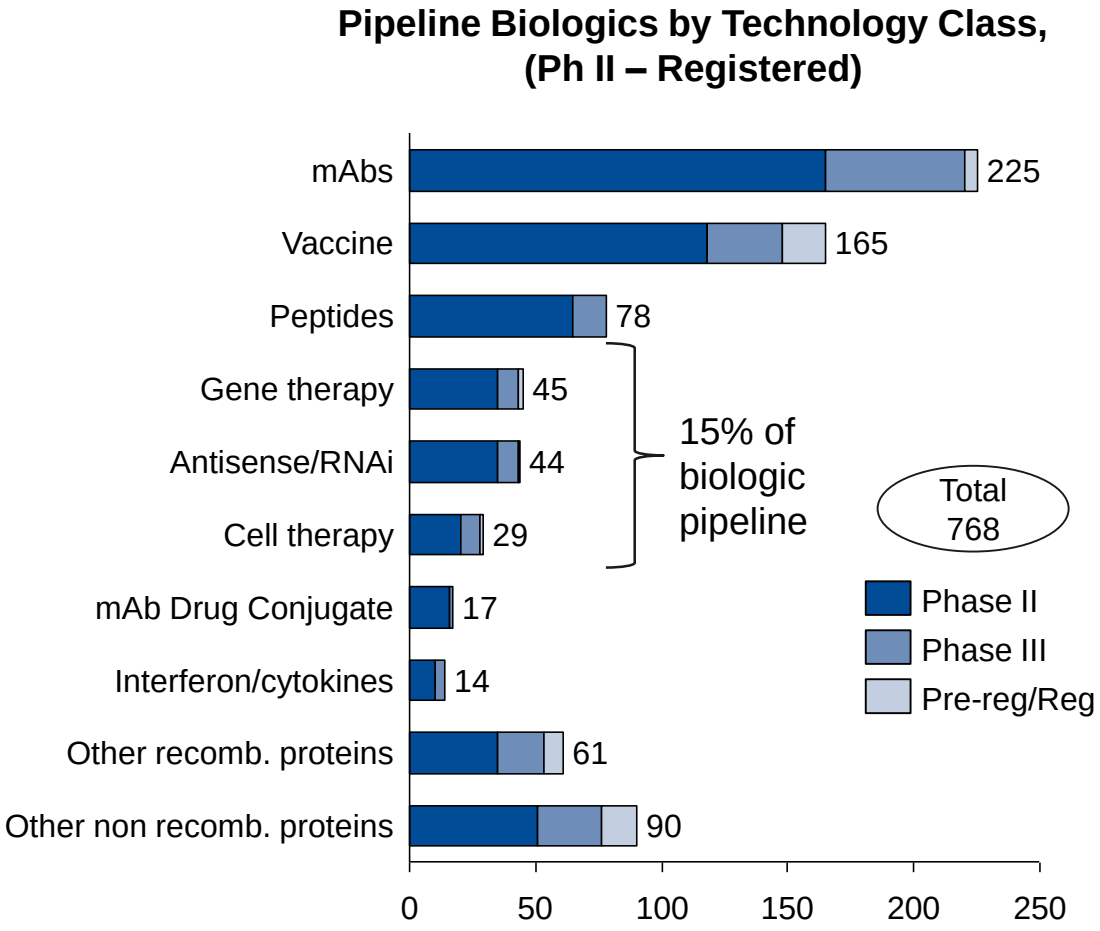


The pipeline has focused on mAbs, but novel therapeutic classes are in trials



Source: QuintilesIMS R&D Focus Dec 2014. Biologic compounds only, Phase II through Registration

Delivery can also be innovative

Intravenous | Subcutaneous | Inhaled | Implanted




Oral | Intranasal | Transdermal (micro needle) | Quick dissolving film

novo nordisk

SANOFI DiCE Molecules

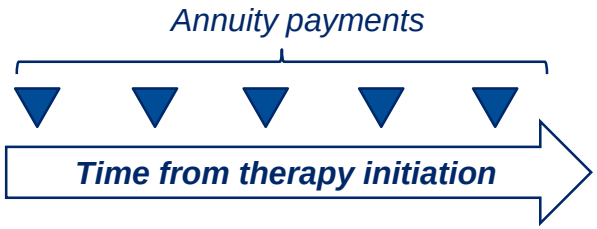


New innovations (often lead by biologics) will challenge the funding status quo

- Timescale of costs: unusual compression of cost
- Upfront cost of treatment vs lifetime benefit
- Individual benefit vs societal benefit
- Outcome uncertainty with new and very novel therapies

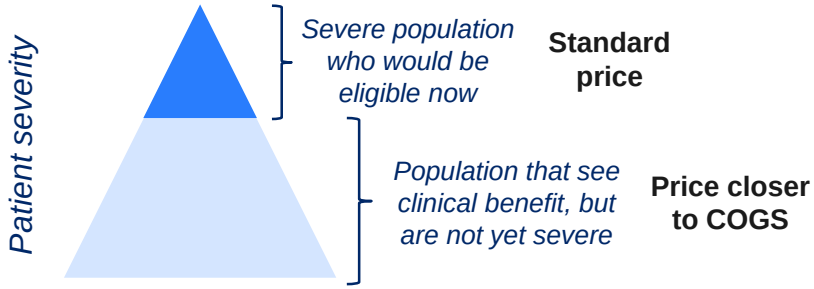
Increasingly, alternative funding mechanisms must be explored

Annuities



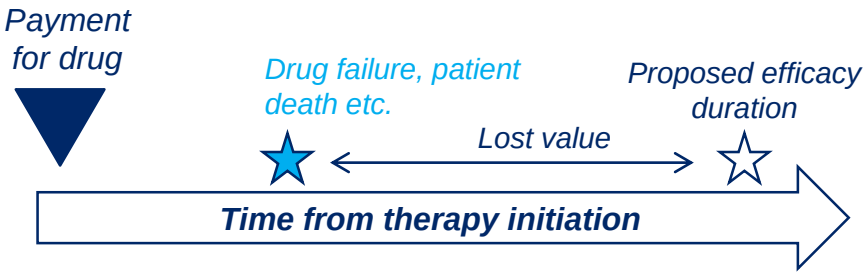
- Upfront payment to manufacturer by 3rd party which then receives annuities from healthcare system for use of product
- Still questions of where risks and product responsibility lie

Differential pricing



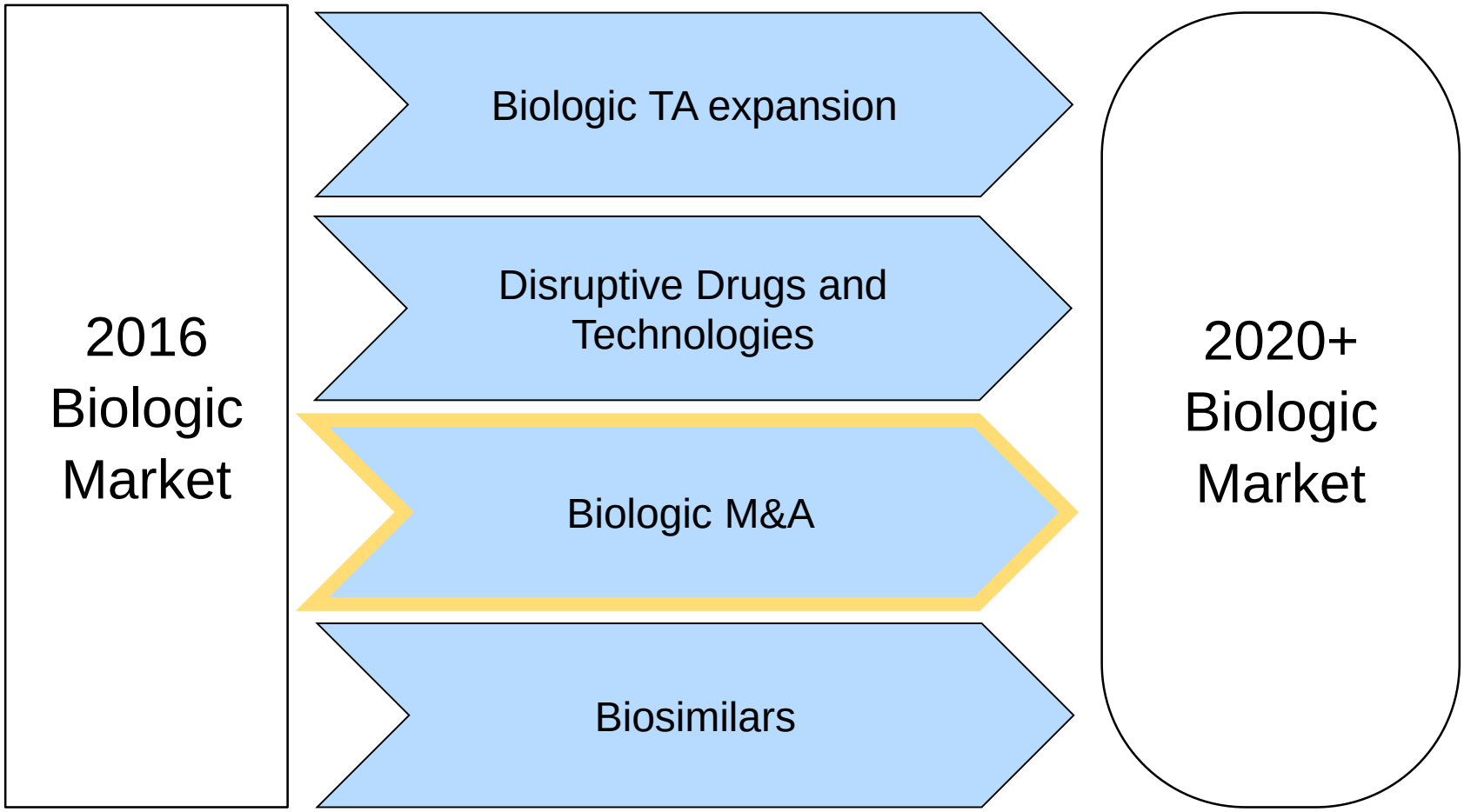
- Widens access to patients who would have treatment restricted
- Could have no data tracking requirements- severe population size agreed before
- Can have multiple tiers

Performance related price



- Based on agreed RWE upon study completion
- Risks if agreement poorly judged or product does not perform as expected

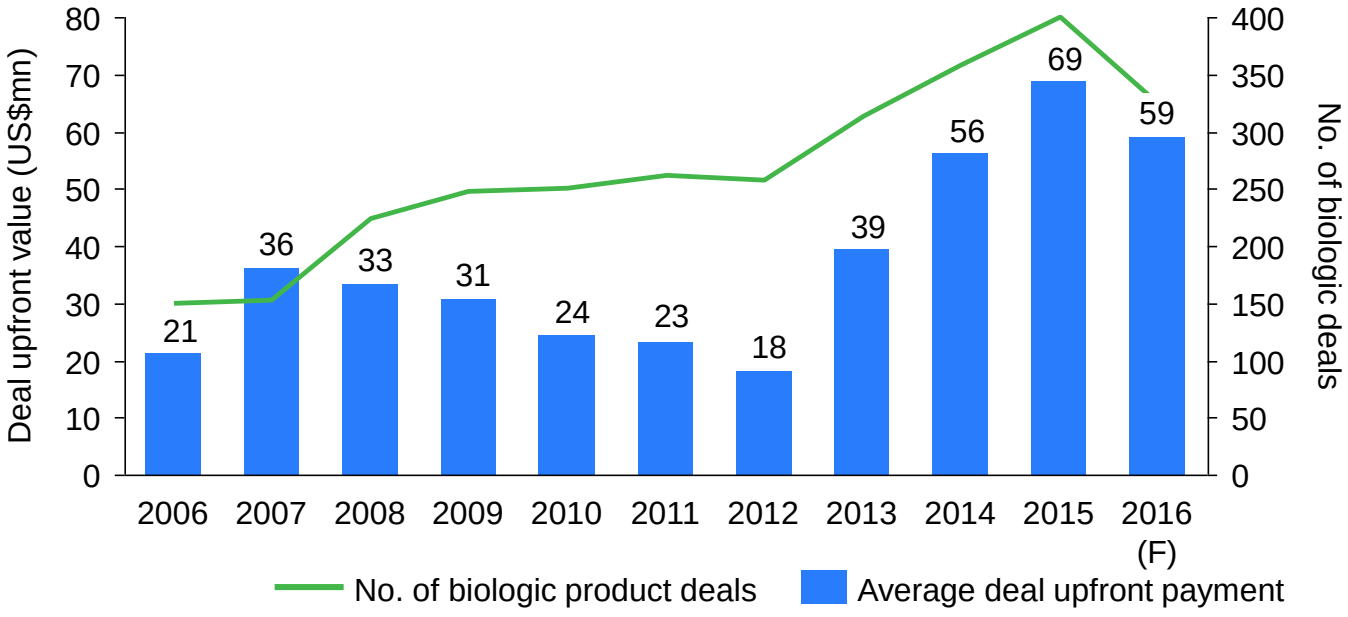
M&A continues as a key biologic market driver



The price to acquire a biologic product tripled between 2012 and 2016

Value and number of biologic pipeline product deals 2006-2016

Deals must be product focused, Most commonly these are Licensing, Collaborative R&D, Technology sharing and M&A



Key drivers in biologic asset demand

- Exciting innovative products with scientific developments
- Biologics have become a established business model
- High availability and low interest rates of capital
- Competition for the best biologic assets is driving up prices

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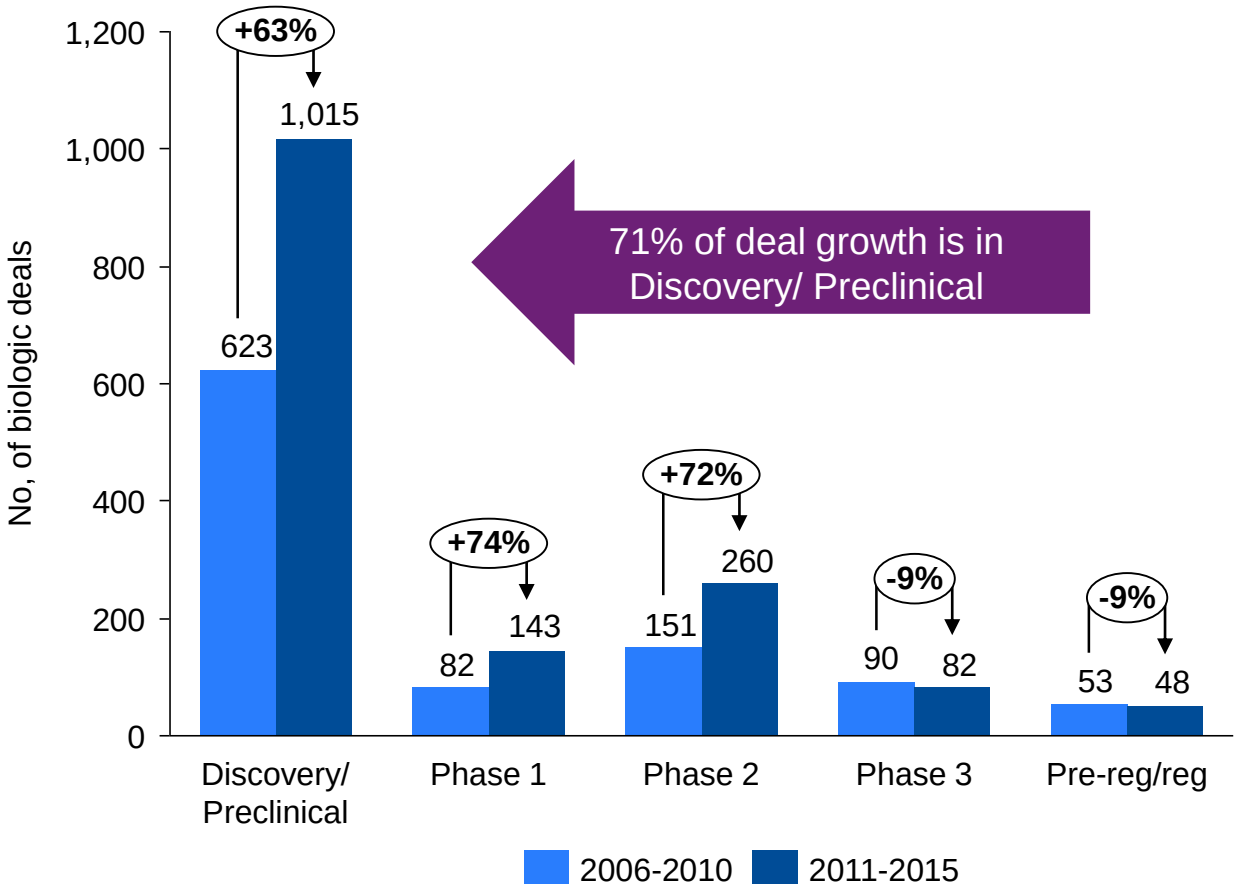
Source: Pharma Deals Nov 2016; 2016 no. of deals extrapolated to the expected full year figure

The increase in deals came from early stage assets

Number of biologic product deals by phase of primary product

2006-10 vs 2011-15



Early deal drivers

- Increased competition for deal making leaves fewer low-hanging late stage assets
- High cost of deals pushes towards early stage development assets
- Pharma has greater comfort in early stage biologic deals
- To balance early stage risk, milestones make up more of the deal value

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Source: QuintilesIMS Pharma Deals Q4 2015

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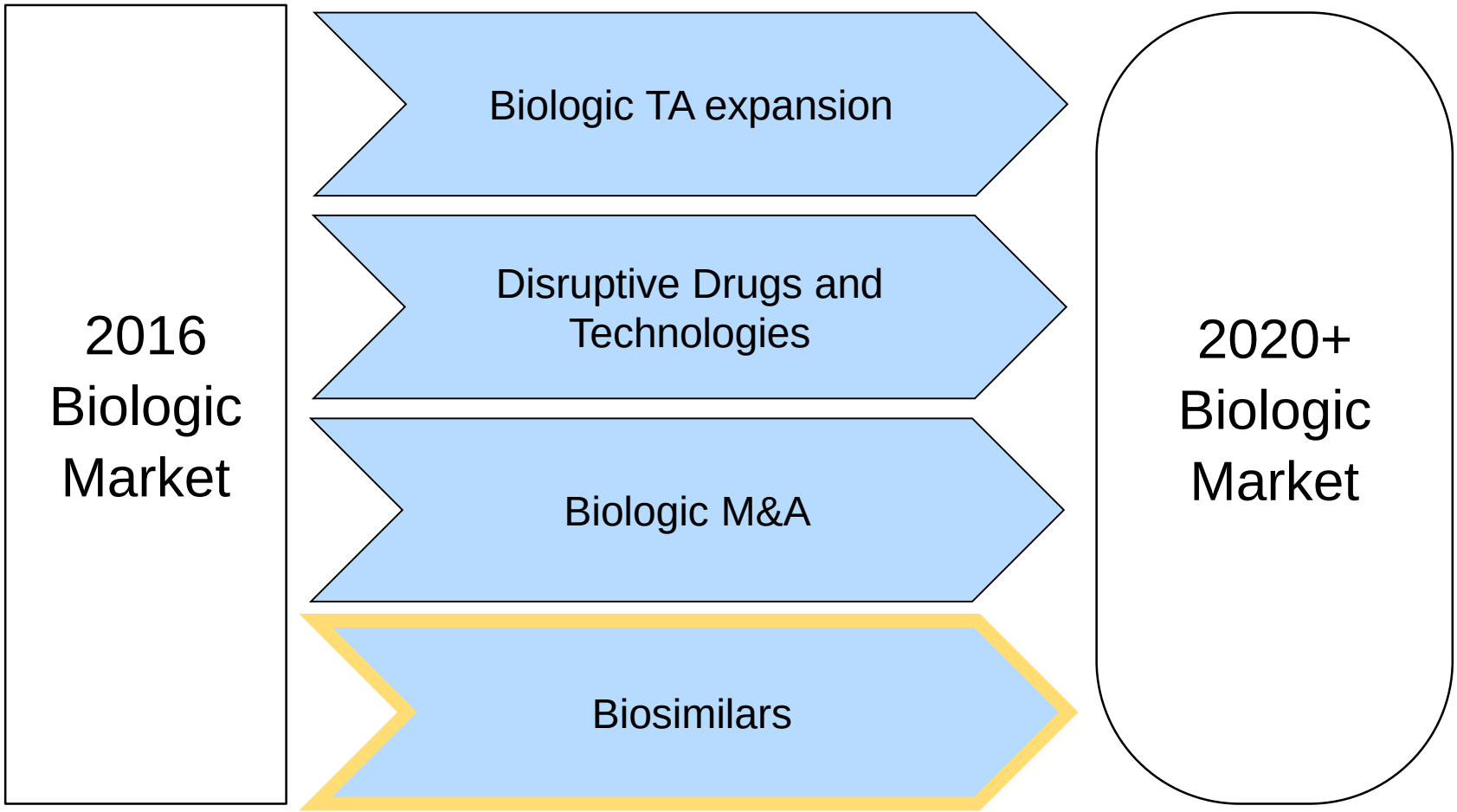
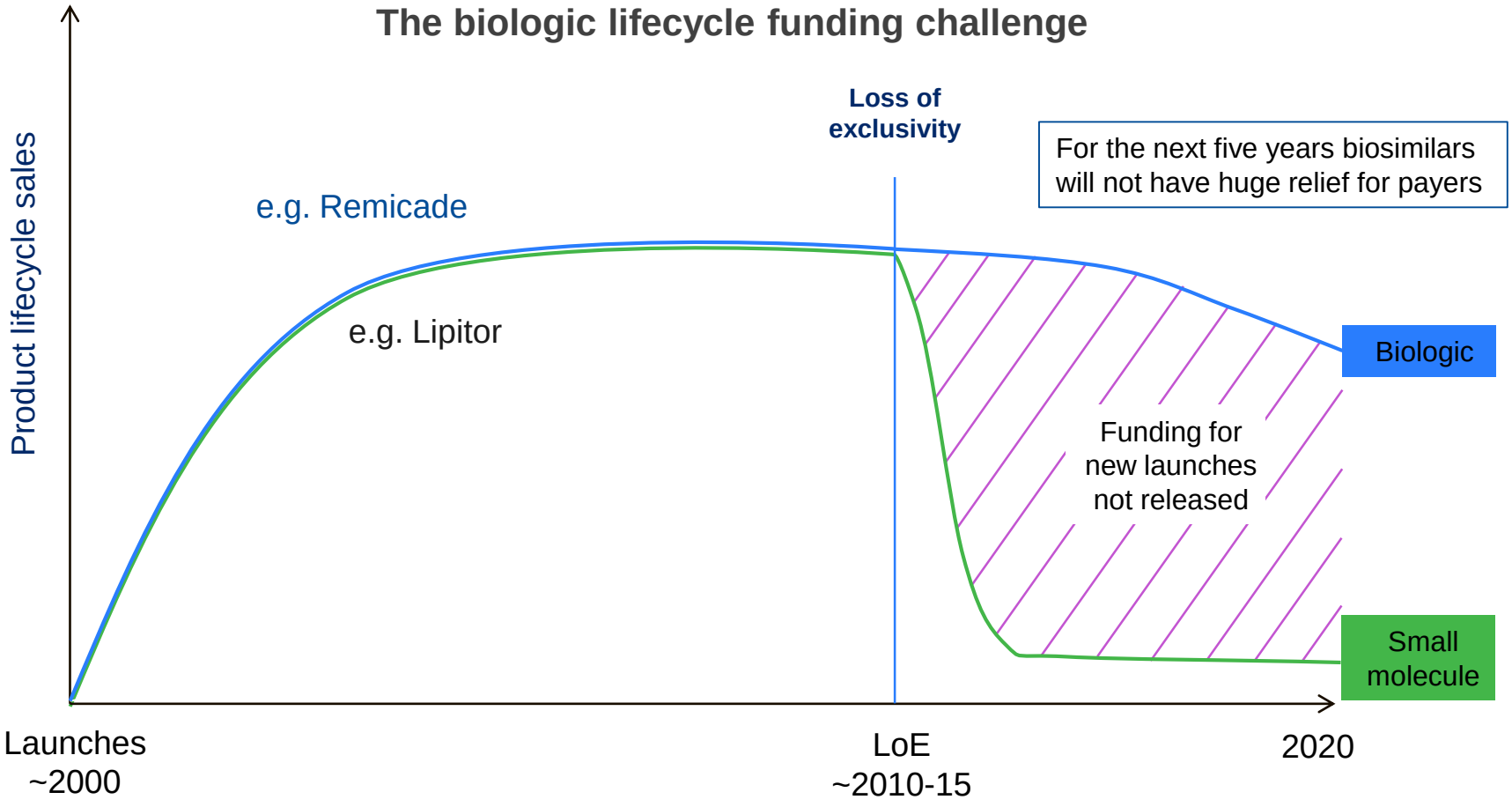


Key blockbuster biologics would have reached a phase of relief for payers (if they were small mol.)

The lack of released funding could disrupt innovative medicine funding



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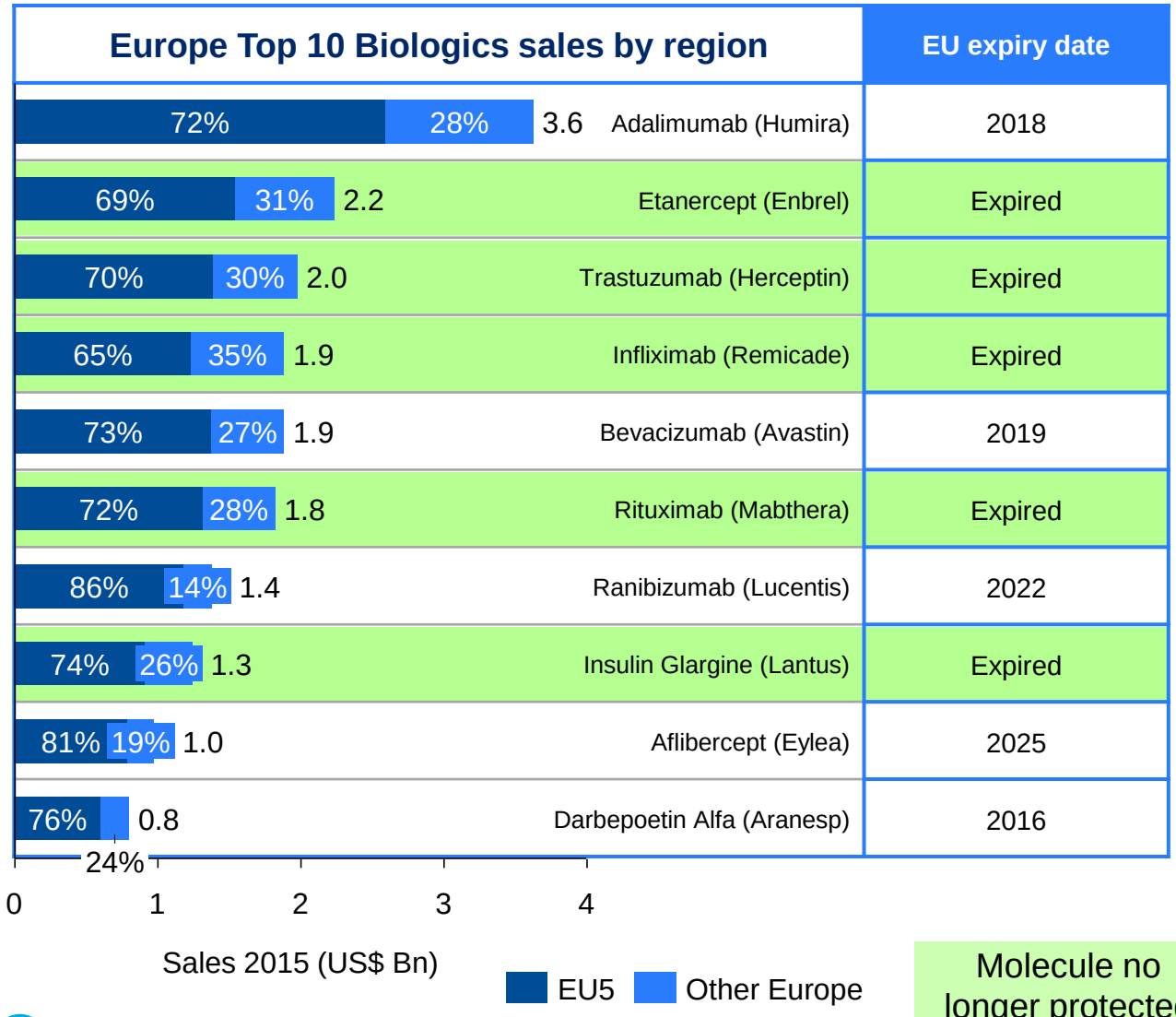
Half the top biologics have lost protection in Europe



Biosimilar delay factors:

- Cost
- Complexity in development
- Patent Uncertainty, Europe wide/local
- Regulatory difficulties and uncertainties

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Source: QuintilesIMS MIDAS Q4 2015; Lovenox excluded

No country has high penetration in all biosimilars, UK and Italy lead EU5

Europe: Biosimilar share of molecule treatment days

	Country	Biosimilar treatment day share (November 2016) infliximab	insulin glargine	etanercept
EU5	UK	60.9%	1.1%	30.8%
EU5	France	27.7%	0.5%	0.7%
EU5	Germany	26.7%	4.9%	16.2%
EU5	Italy	46.0%	11.6%	0.8%
EU5	Spain	32.9%	6.6%	0.2%
High penetration EU	Finland	92.1%	0.9%	-
High penetration EU	Norway	95.6%	1.8%	69.0%
High penetration EU	Poland	97.7%	31.5%	0.0%
High penetration EU	Denmark	97.8%	4.0%	78.7%

High uptake

Low uptake

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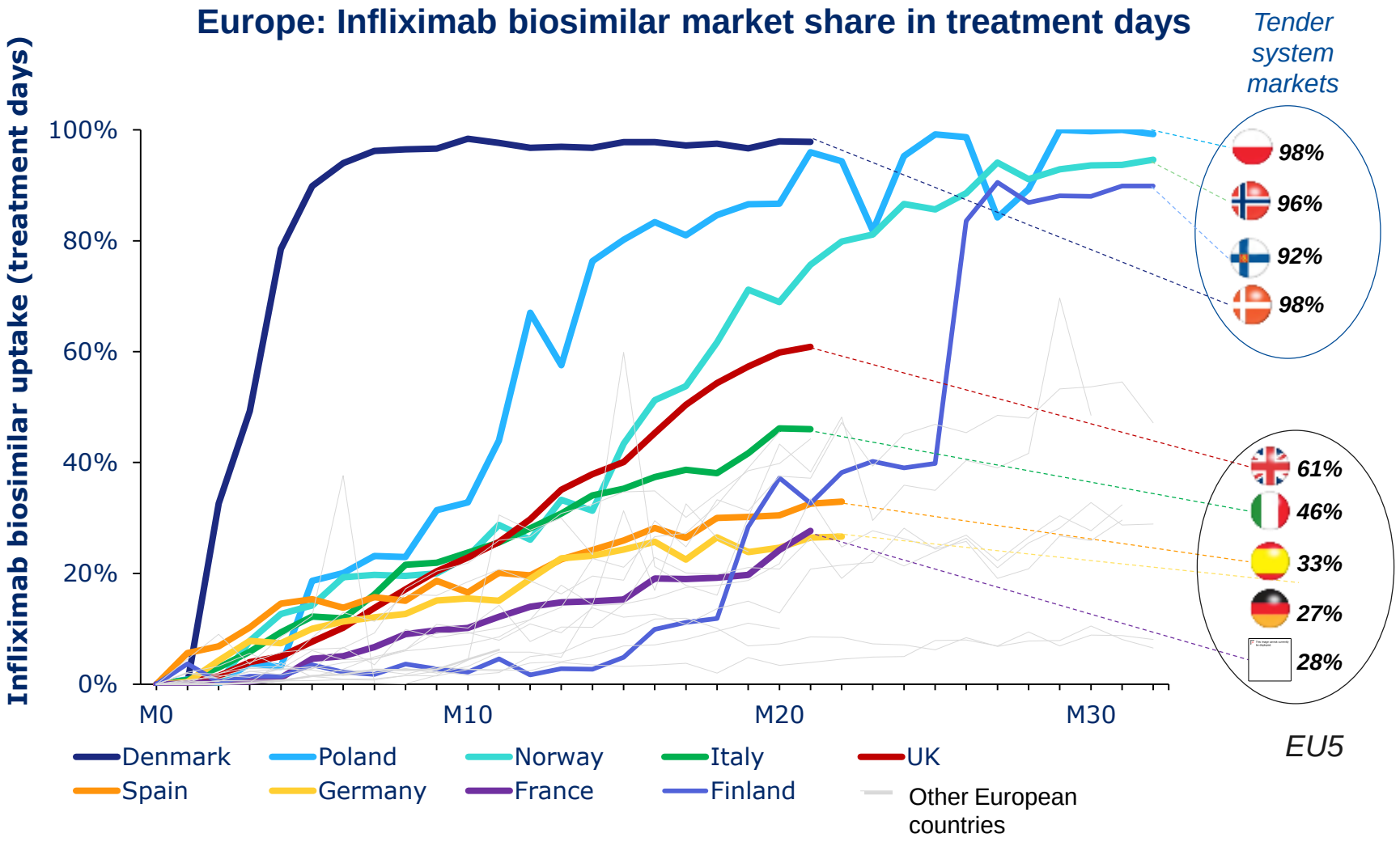
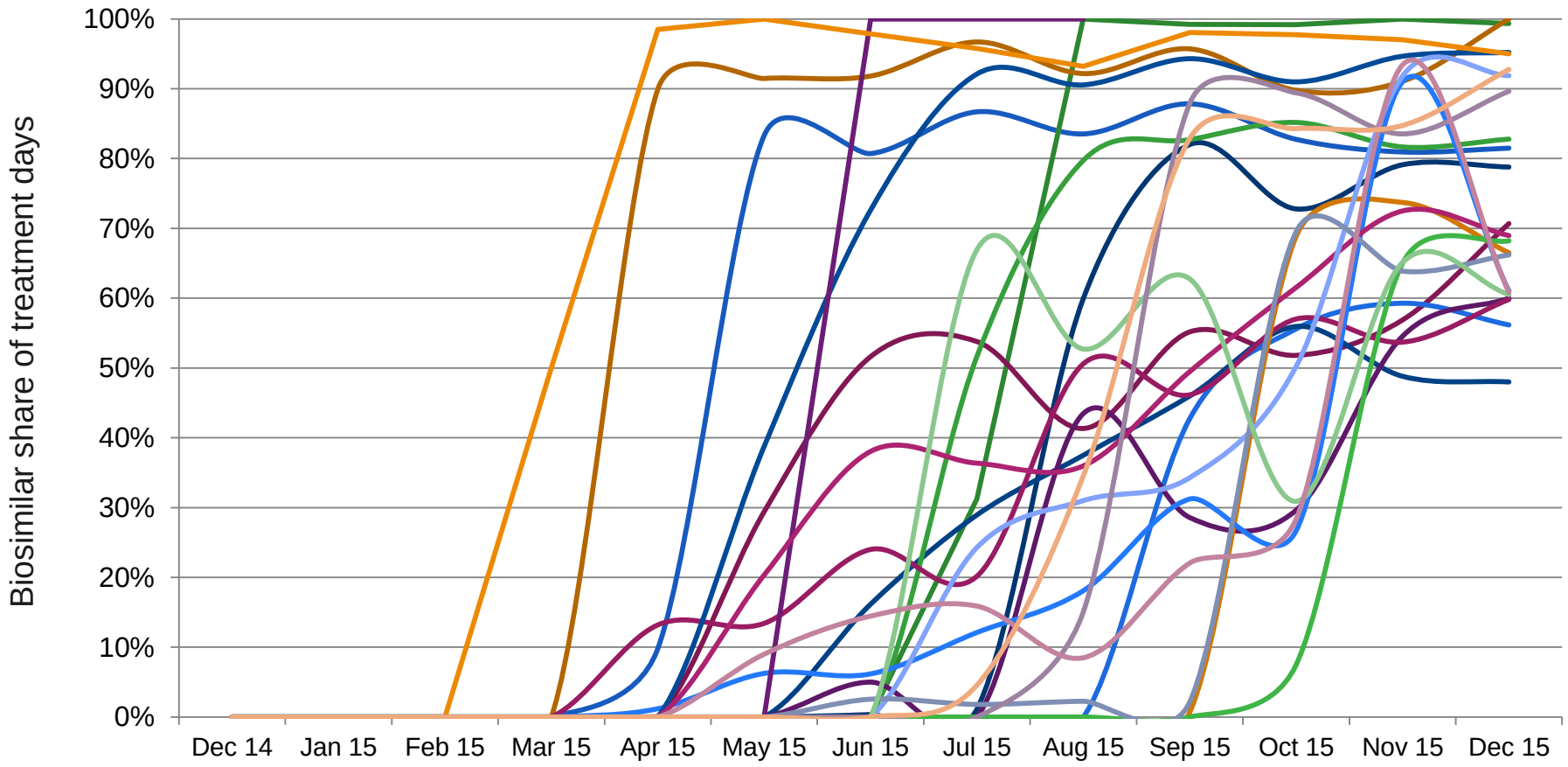
Source: QuintilesIMS MIDAS MTH Nov 2016

For Infliximab, the top 5 European countries do not lead



Source: QuintilesIMS MIDAS MTH November 2016 ; Denmark data from MIDAS Monthly Restricted database; Latvia excluded because only biosimilar manufacturers present in market

But national data can hide a more complex subnational picture



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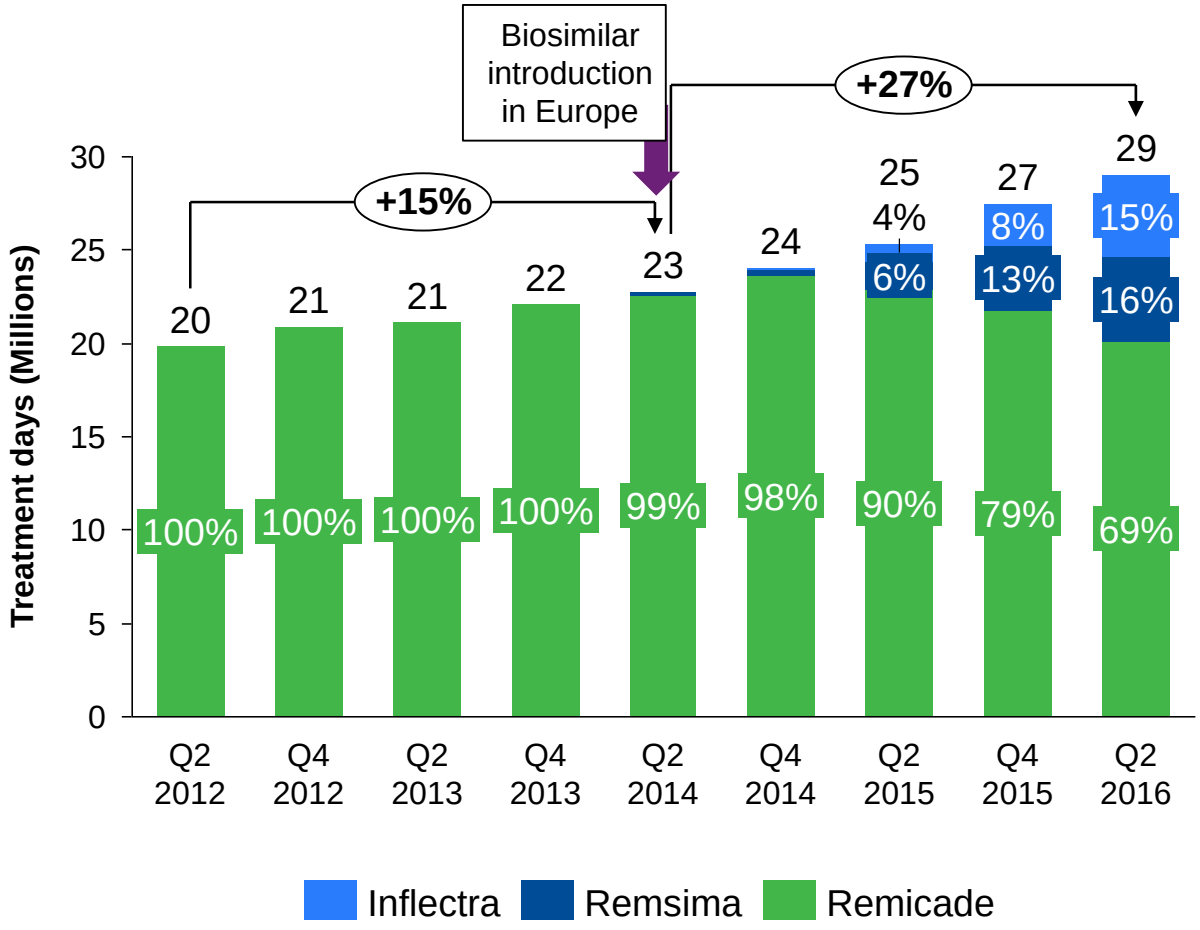
Source: QuintilesIMS UK data Q4 2015

Infliximab usage increases post biosimilar entrance

Europe: Treatment increase as a result of biosimilar usage



Country	Infliximab TD % increase Q2 2012- Q2 14	Infliximab TD % increase Q2 2014- Q2 16
France	16%	35% ↑
Germany	25%	22% ↓
Spain	0%	25% ↑
Italy	6%	9% ↑
UK	27%	27% ↔
Norway	19%	56% ↑
Finland	12%	45% ↑
Europe	15%	27% ↑

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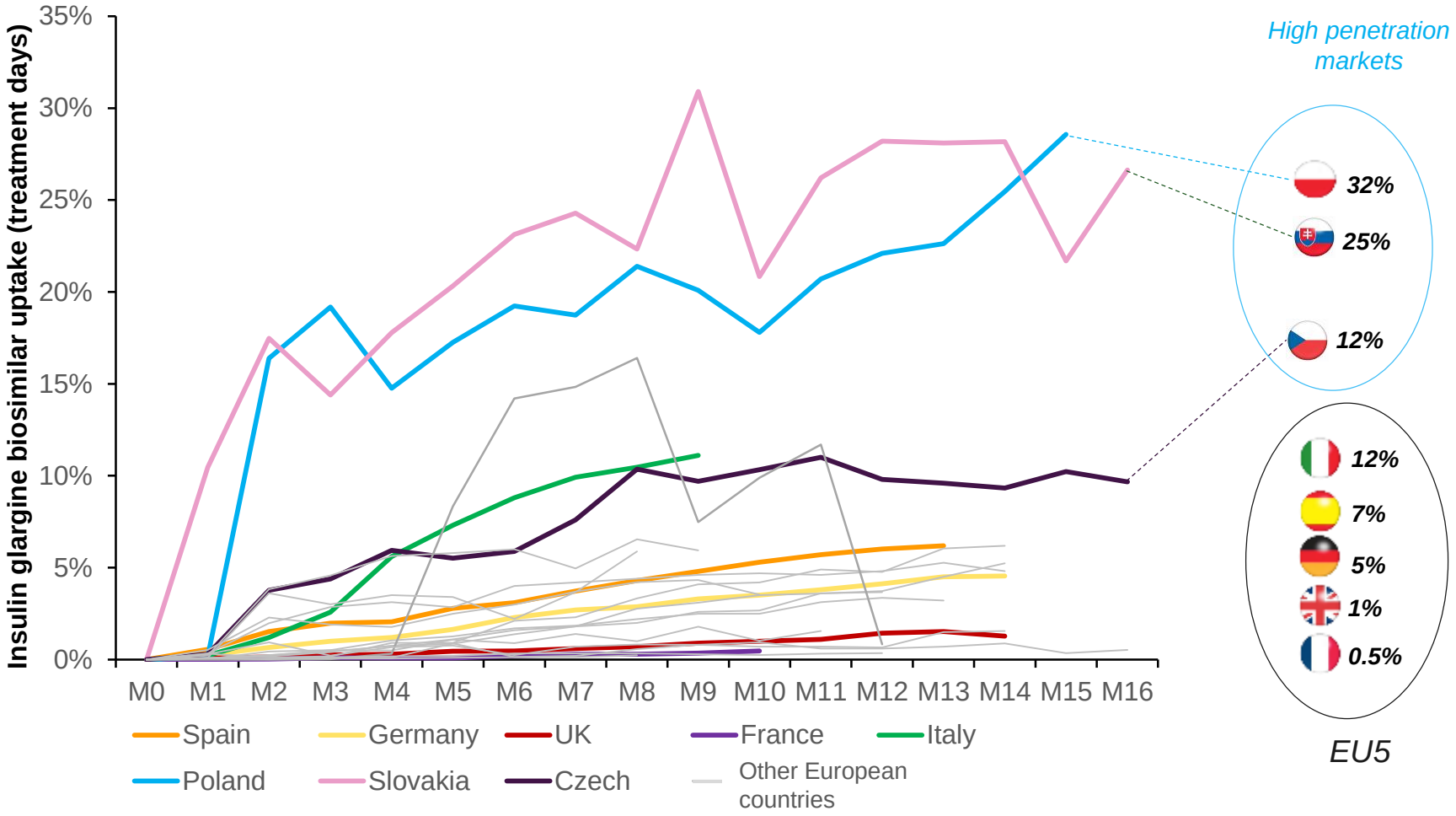
Source: QuintilesIMS MIDAS Q2 2016

Insulin biosimilars low penetration in EU5 countries

Europe: Insulin glargine biosimilar market share in treatment days



Source: QuintilesIMS MIDAS MTH November 2016, Denmark data from MIDAS Monthly Restricted database

Oncology will be next

Europe: Recent biosimilar filings

Originator Name (molecule name)	Therapeutic area	Total pending EMA applications	Originator protection expiry	European Revenue 2016 (Bn €)
Enbrel (etanercept)	Autoimmune	2	Aug-2015	€2.0 Bn
Lantus (insulin glargine)	Diabetes	1	May-2015	€1.1 Bn
Herceptin (trastuzumab)	Oncology	2	Jul-2014	€1.8 Bn
Mabthera (rituximab)	Oncology	2	Feb-2013	€1.7 Bn
Humira (adalimumab)	Autoimmune	3	Apr-2018	€3.4 Bn
Neulasta (pegfilgrastim)	Oncology	4	Aug-2017	€0.5Bn

Source: EMA website June 2016; *Launched biosimilars have not been included*

Biosimilar conclusions

Each country has its own story, but only one direction

Stakeholders are making decisions which will have lasting impact

Countries can increase usage while reducing costs

Early planning of follow-on innovation is key

Disruption and maturity: the next evolution of biologics

A market reaching maturity

- The impact of biosimilars will bring market growth dynamics in line with small molecules
- The competitive field has expanded, we have entered the era of me-too biologics
- Select biologic markets are relatively satisfied
- Players are more comfortable with biologic deal making and are willing to take greater risks

A market awaiting disruption

- Biologics entering new high potential TA's
- Biosimilar entrance will disrupt the top biologic players, refreshing the score sheet
- Breakthrough innovation in the pipeline threatens current treatment paradigms