Biotechnology Development Trends - Overview

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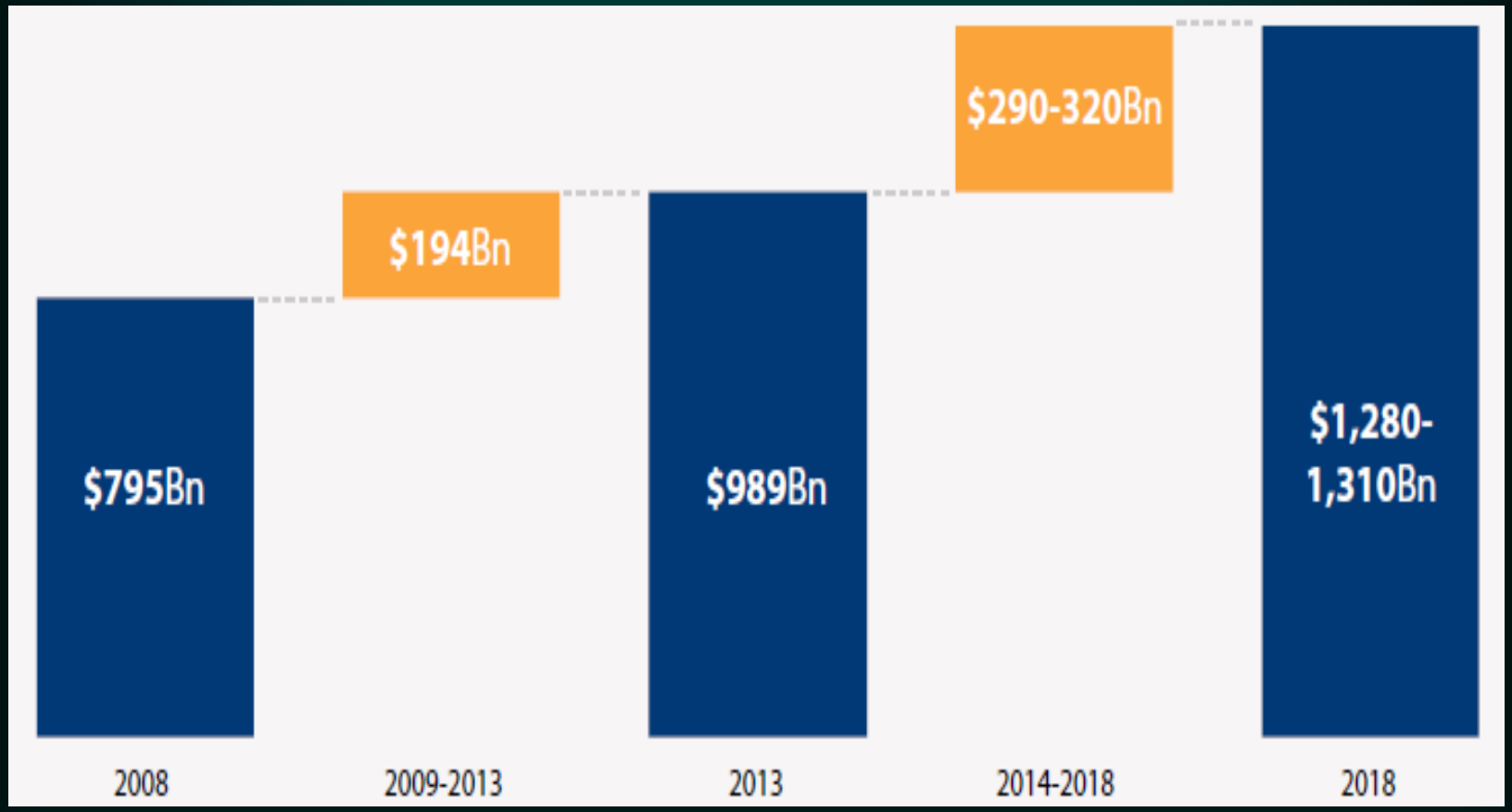
- The field
- Oncology therapeutics
- Oncology vaccines
- Biologics/mAb's
- Biosimilars – US & EU
- Drug Development trends

Global pharmaceutical market

$ 1 Trillion – 2014

$ 1.3 Trillion => 2018



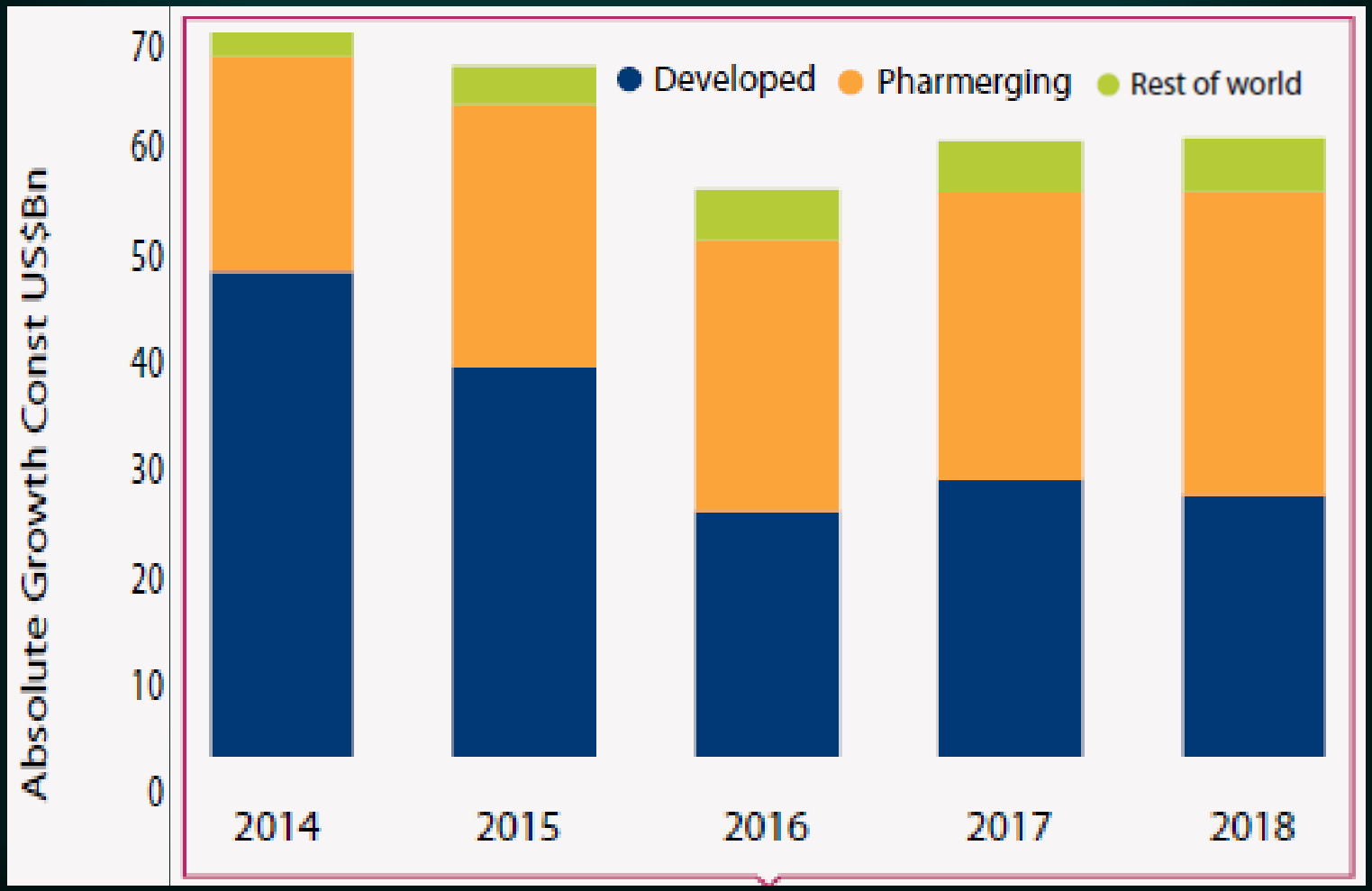
IMS Health -2015

Global pharmaceutical top markets 2013

Country	Rank	$ Bn	Growth (%)
USA	1	340	4
Japan	2	94	-16
China	3	87	16
Germany	4	46	9
France	5	37	1
Brasil	6	31	5
Italy	7	28	6
Canada	8	25	16
UK	9	21	-3
Spain	10	21	4

IMS Health -2014

2014 -2018 Growth $ 305 – 335 Bn Forecast



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- **Developed: U.S., Japan, Germany, France, Italy, Spain, U.K., Canada, South Korea.**

- **Pharmerging: China*, Brazil, Russia, India, Algeria, Argentina, Colombia, Egypt, Indonesia, Mexico, Nigeria, Pakistan, Poland, Romania, Saudi Arabia, South Africa, Thailand, Turkey, Ukraine, Venezuela, Vietnam.**

China* represents 46% of the pharmerging market

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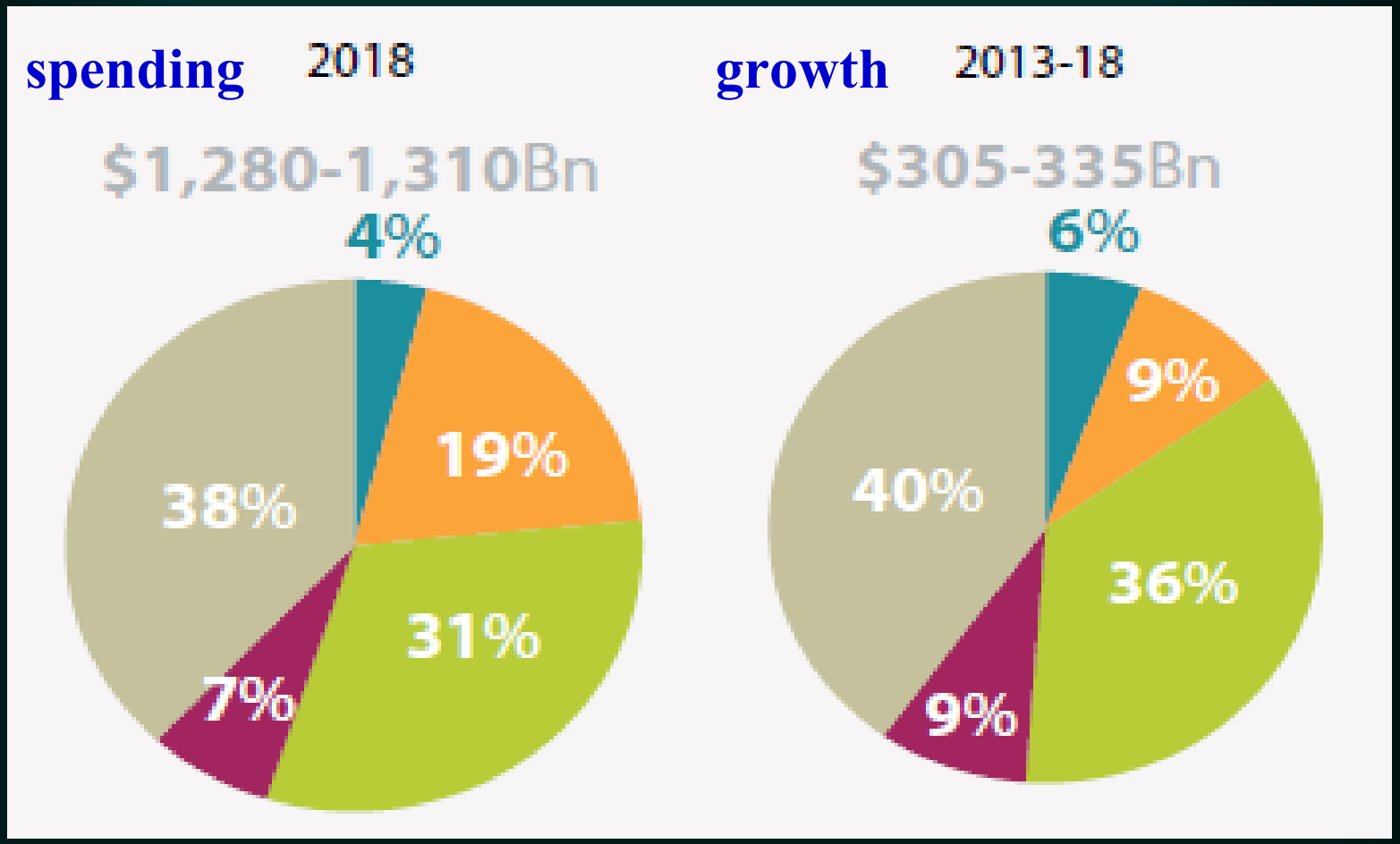
Geographic distribution of spending & growth



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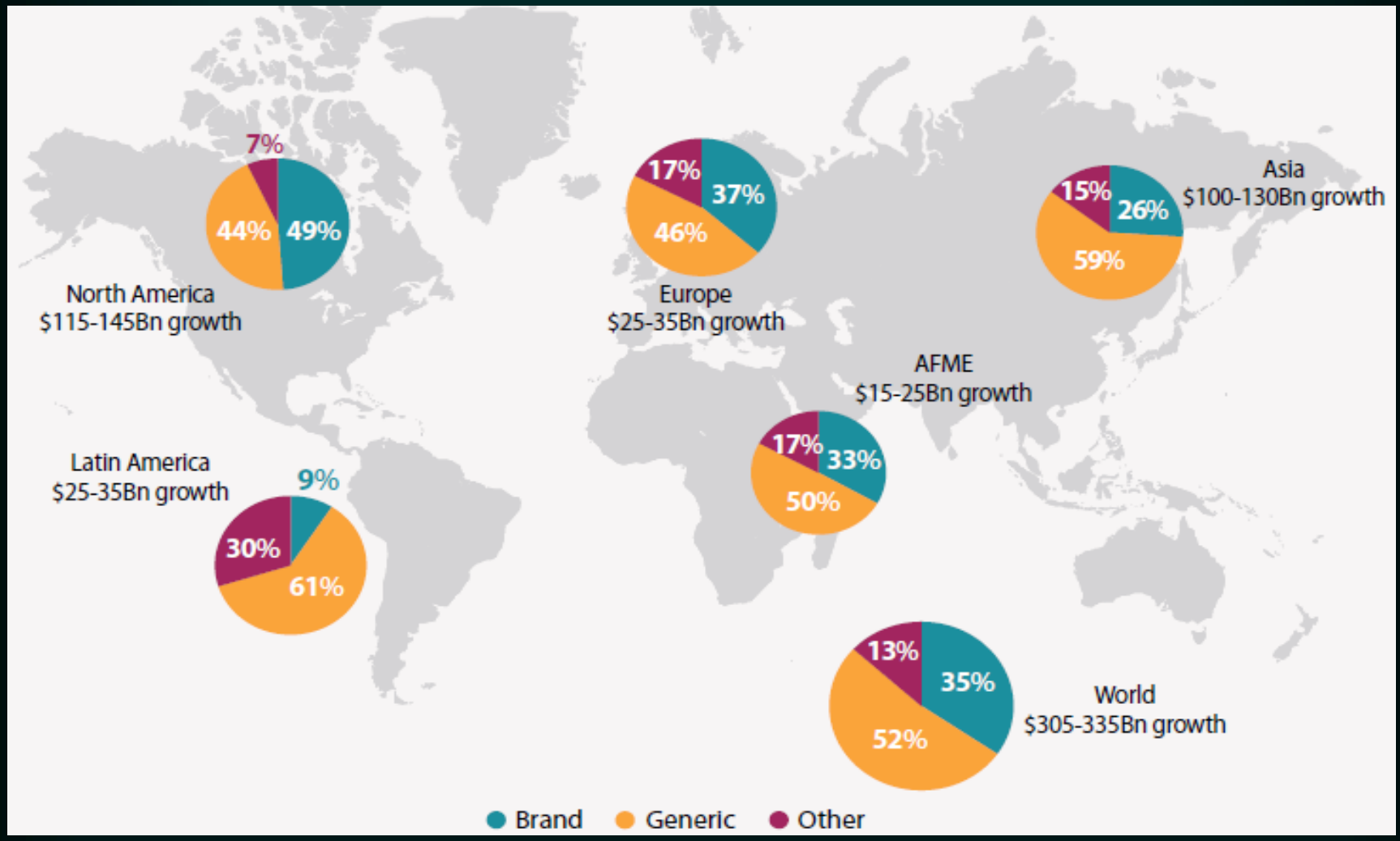
Geographic distribution of medicine growth

Brand vs Generic



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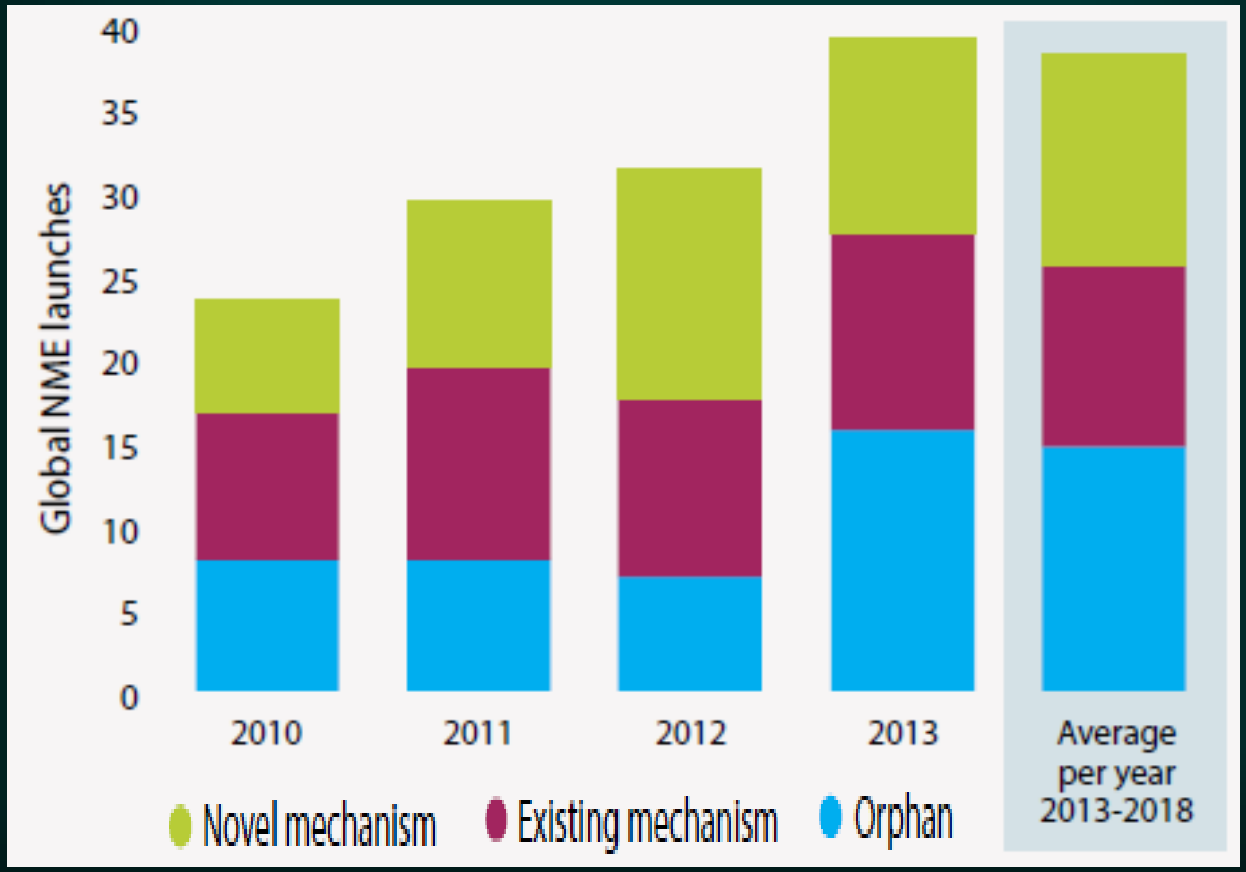
Global launch of new molecular entities (NMEs)



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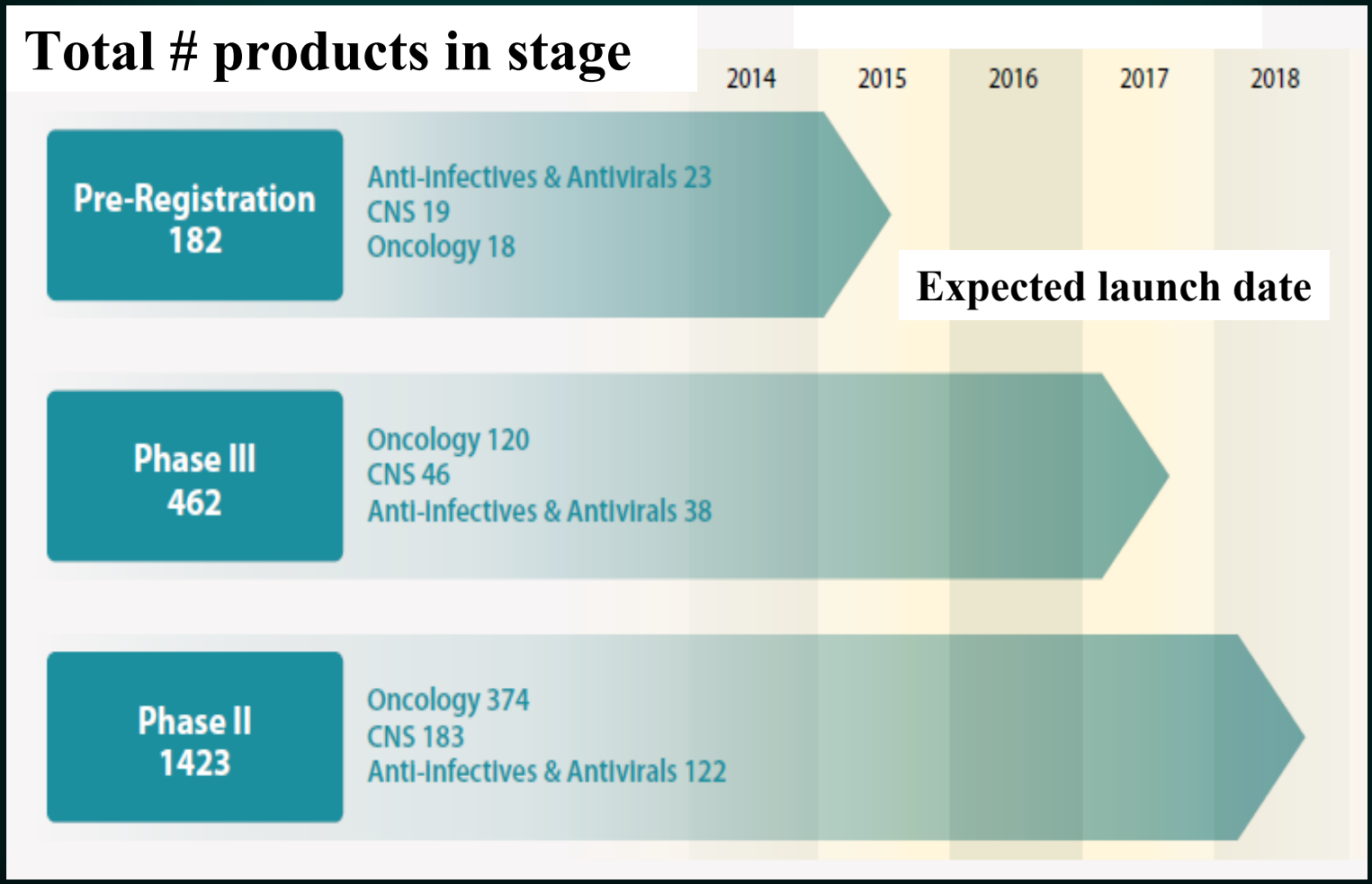
Number of products in pipeline

by phase and therapy area



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Global pipeline highlights

- **Oncology** 31% of the total pipeline globally , 25% of the late-stage pipeline (Phase II through pre-registration), and is double the size of the next highest class.
- **CNS** focus on mental health, multiple sclerosis and neuropathy indications.
- **Anti-infectives** focused around HIV and hepatitis C
- **The top three classes** in the late-stage pipeline constitute 46% of the total late phase pipeline.
- **Biologics** - 36% of the late-stage pipeline and 45% of the late stage oncology pipeline.

IMS Health -2015

Global cancer medicines

- Global cancer market sales $65 Bn in 2013
- Overall market spending - $100 Bn* in 2018
- Main growth anticipated in targeted therapies and biologics

* **Hepatitis C treatments ~ 100Bn not included**

Source: IMS Health Institute 2014

The global market for cancer treatments and diagnostics

$ bn - 2013 to 2018

	$17.8 bn in 2013
uterine	$21.6 bn in 2018
	(CAGR)* of 3.9%
	$11.6 bn in 2013
cervical	$15.6 bn by 2018
	(CAGR)* of 6.1%
	$29.3 bn in 2012
prostate	$50.3 bn in 2017
	(CAGR)* of 11.4%

* compound annual growth rate

BCC Research LLC

Antibody Drug Conjugates (ADC)

global market

$179 million in 2012

$396 million in 2013

$2.8 billion in 2018

(CAGR)* of 48.1%

* compound annual growth rate

BCC Research LLC

APPROVED ADC's

- **MYLOTARG (GEMTUZUMAB OZOGAMICIN) - Wyeth**
  acute myelogenous leukemia from 2000 to 2010
  mAb to CD33 linked with calicheamicins
  Pfizer withdrew Mylotarg 2010, second chance in combination

- **ADCETRIS (BRENTUXIMAB VEDOTIN) - Seattle Genetics**
  Hodgkin lymphoma 2011 approved, mAb to CD30
  cathepsin-cleavable linker + monomethyl auristatin E

- **KADCYLA (TRASTUZUMAB-DM1) – Genentech**
  HER2 positive breast cancer 2013 approved, mAb Herceptin
  to HER2 + SMCC linker + maytansinoid (DM1)

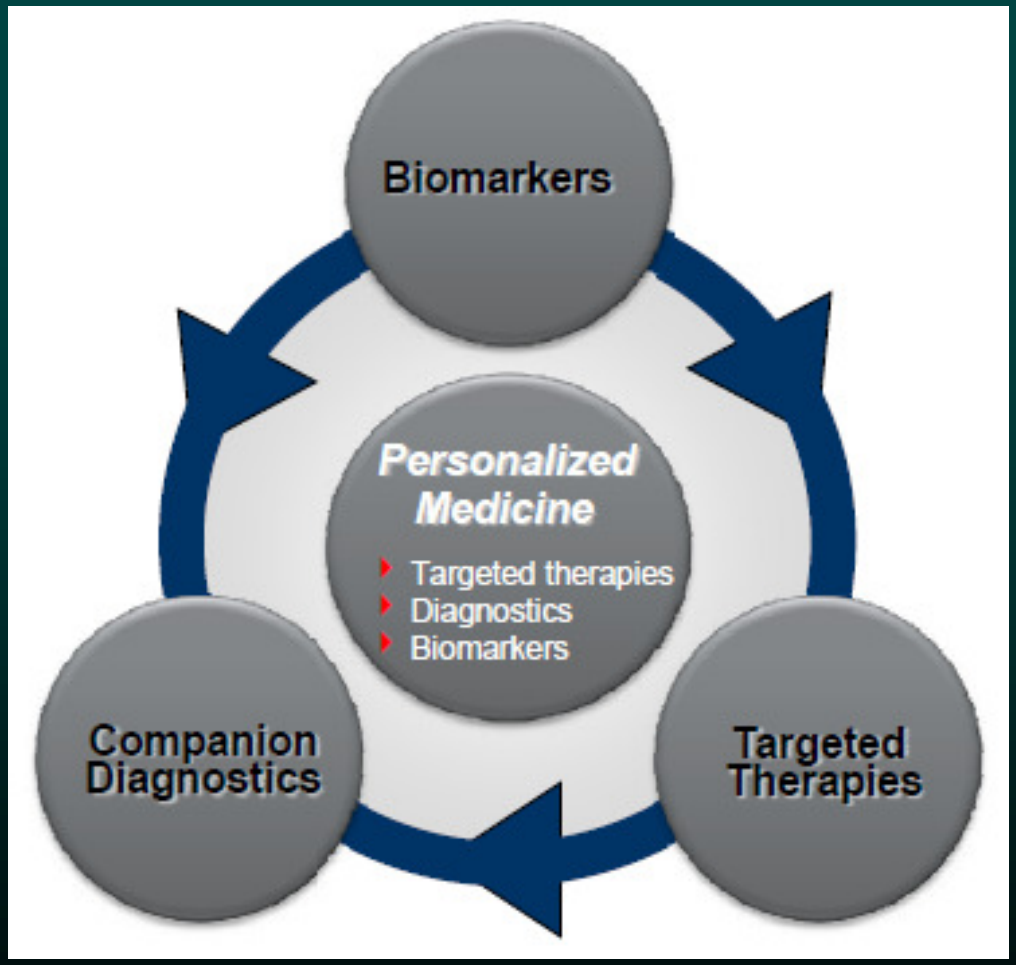
ADC CYTOTOXINS

- **Calicheamicin**
- **Maytansinoid**
- **Auristatins (MMAE, MMAF)**
- **PBD's (pyrrolobenzodiazepines)**

KEY ANTIGEN TARGETS FOR ADC's

- HER2
- Nectin-4
- Mesothelin
- GPNMB
- PSMA
- EGFR
- VEGF
- CD19
- CD20
- CD22
- CD25
- CD30
- CD33
- CD40
- CD56
- CD74
- CD79a and CD79b
- CD138
- CEACAM
- SLITRK6
- LIV-1
- EGP-1
- Mesothelin

Growing oncology complexity



Cancer vaccines – structure

1990 – 2012 in US (191 analyzed)

- Cell based - 70%
- Biologics - 40%
- Synthetic peptides - 20%
- Gene therapy - 15%

Drug Discovery Today -2012

Cancer vaccines - approved

- **Melacine -** melanoma therapeutic - Corixa(GSK)
- **Gardasil** - cervical preventive - Merck
- **Cervarix** - cervical preventive - GSK
- **Provenge** - prostate therapeutic - Dendreon

Cancer vaccine global matket

Forecast

$4.5 billion in 2013,

$4.0 billion in 2014

$4.3 billion in 2019

(CAGR) of 1.3% - 2014-2019.

BCC Research 2015

Cancer vaccine players

Accentia
Antigenics
AVAX
GlaxoSmithKline
BioVex
Immatics biotech
Merck & Co.
Northwest Biotherapeutics
Oncothyreon
Vaccinogen
Bavarian Nordic
Celldex
Immunocellular Therapeu.

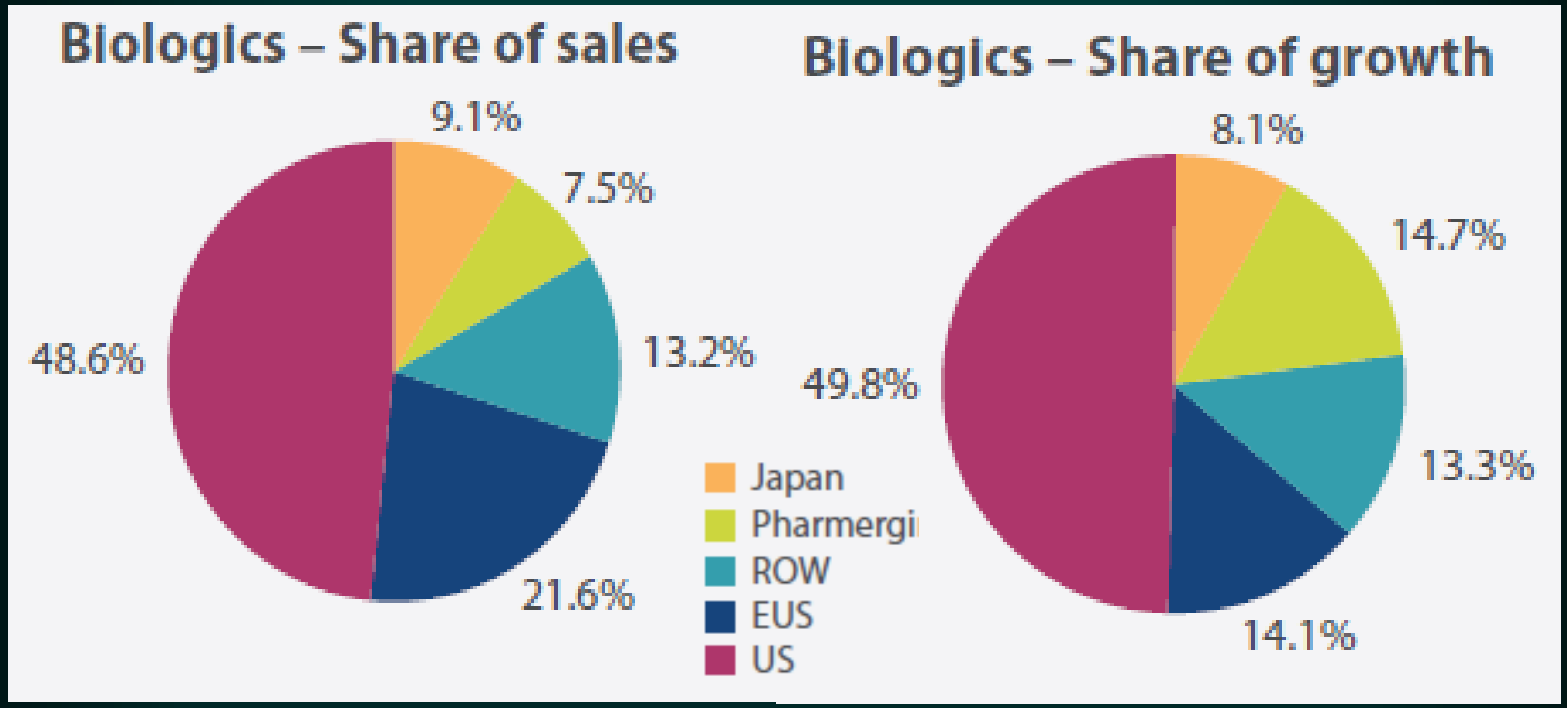
Highest competition

- melanoma,
- lymphoma,
- cervical,
- renal
- prostate cancer

Many of the products already in Phase III development have SPA, fast track status, or orphan drug

Global biologics positions – 2012

$ 170 Bn



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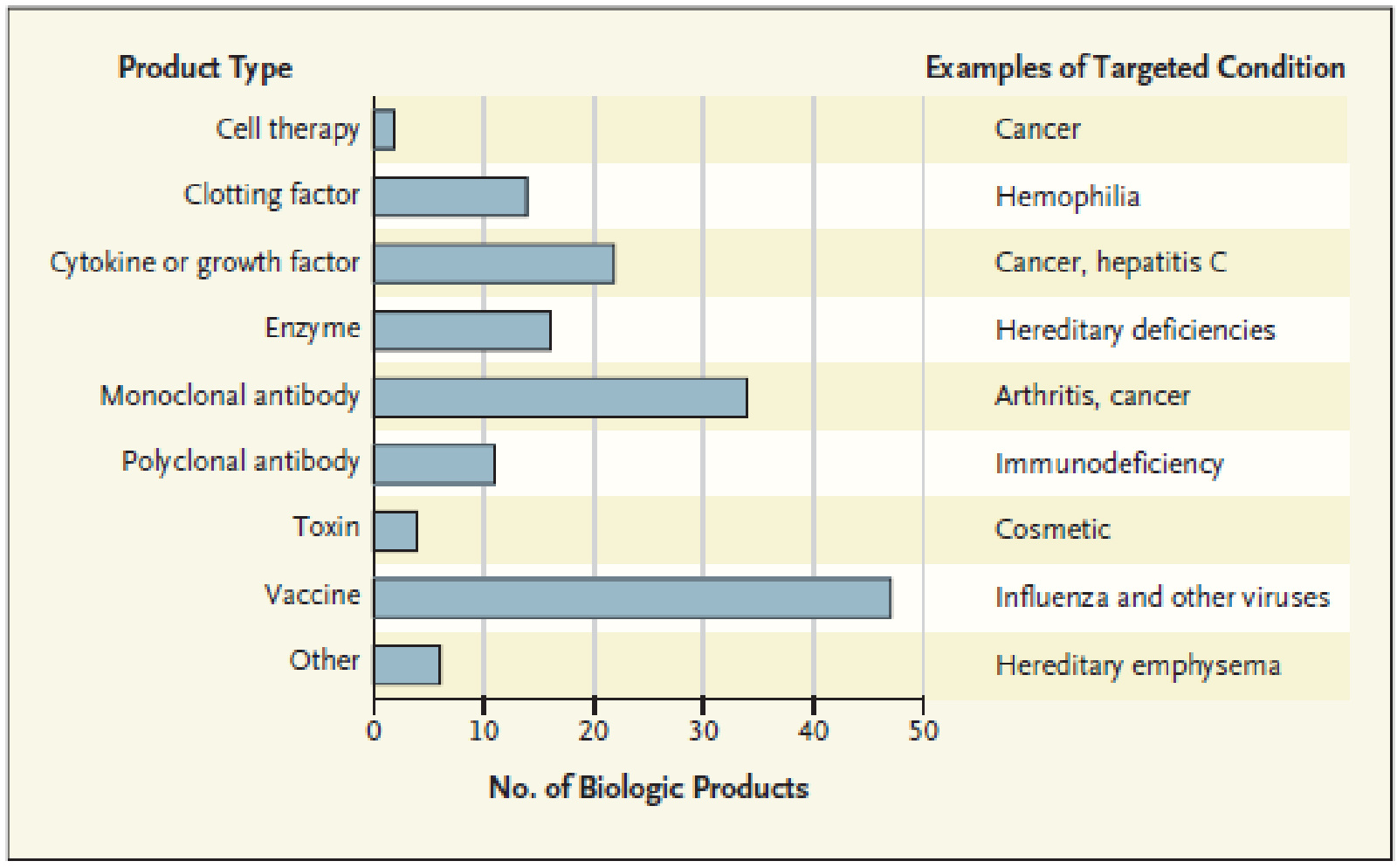
FDA approved biologics

CDER – 138 as 10/2017



Kozlowski *et al.*, *The New England Journal of Medicine*, 365:5, 385-88, 2014

The Global Biologics Market

- Over the past 30 years, growing at twice the rate of the market as a whole.
- The global biologics market reached nearly $170 billion in sales value in 2012, accounting for 18 % of the overall market.
- And five of the top 10 global products in terms of sales volume are biologics, up from just two in 2008.

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Top 10 pharmaceutical products by sales
worldwide in Bn $ - 2014

Drug	$ Bn
Humira*	11.84
Lantus*	10.33
Sovaldi	9.38
Abilify	9.29
Embrel*	8.71
Seretide	8.65
Crestor	8.47
Remicade*	8.1
Nexium	7.68
Mabthera*	6.55

Statista.com 2015

- In 2001 biotech products generated 7% of revenue by the 10 top selling pharmaceutical-biotech products worldwide, in 2012 accounted for 71% of the 10 top selling products.

- In 1989, only 13 biotechnology products were commercially available. By 2012, that number had grown to 210.

Tufts Center for the Study of Drug Development 2013

Large pharma's do develop biologics

- The number of biotech products in clinical trials grew 155% in 11 years, from 355 in 2001 to 907 in 2012, with Big Pharma in 2012 engaged in about 40% of all biotech products in clinical development.

- Financing of biotech research increased nearly 10-fold in a decade, from $10.5 billion in 2001 to $103 billion in 2012.

- Worldwide growth in biotechnology product sales between 2001 and 2012, from $36 billion to $170 billion.

Tufts Center for the Study of Drug Development 2013

Patent expirations

- 12 biologic compounds that generate $72 billion in sales face patent expiration.
- They represent 40 % of the global biologic market today & include Humira®, Enbrel®, Remicade®, Lantus® & more.

TOP BIOLOGIC PATENT EXPIRATIONS

Biologic	Global sales $ bn	Expiry Date	
		EU	US
Adalimumab (Humira)	11.8	2018	2016
Insulin Glargine (Lantus)	10.3	2014	2014
Etanercept (Enbrel)	8.7	2015	2028 (extended)
Infliximab (Remicade)	8.1	2015	2018
Rituximab (Mabthera)	6.6	2013	2016
Bevacizumab (Avastin)	5.6	2019	2017
Insulin Aspart (Novomix, Novorapid)	5.4	2015	2015
Interferon Beta-1A (Avonex, Rebif)	5.4	Expired	Expired
Trastuzumab (Herceptin)	5.1	2014	2019
Glatiramer Acetate (Copaxone)	4.7	2015	2014
Pegfilgrastim (Neulasta)	4.2	2015	2014
Ranibizumab (Lucentis)	4.2	2016	2016

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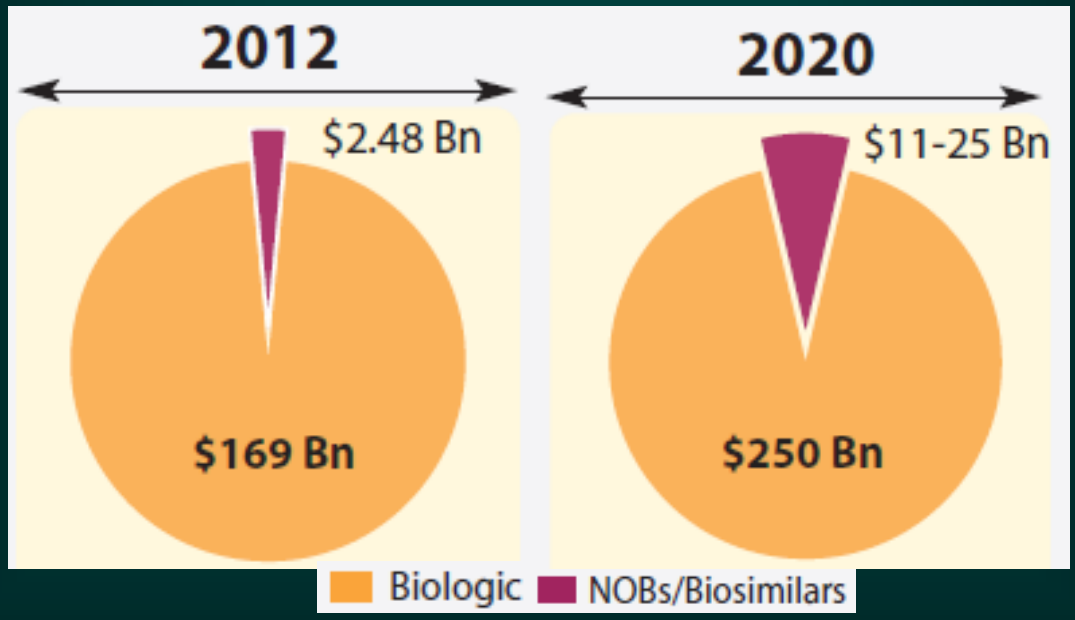
FORECAST FOR BIOLOGICS & BIOSIMILARS



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Market trend

- Biologic sales will top $200 billion annually by 2016-2017, $250 billion by 2020, with antibodies as a market leader
- Biosimilar market will reach 4-10% of $10-25 billion by 2020
- Biosimilars can't claim 10 percent of global biologics sales without a strong U.S biosimilars market

IMS Health -2015
Fish & Richardson 2013

Cost

- Biosimilar development costs are 50 times higher than generic small molecule
- Over the next decade, biosimilars could save more than $40 billion in worldwide biologics spending, as biosimilar pricing is expected to be 15% to 35% less than originator biologics pricing.

What

- Insulin products
- Growth hormones
- Erythropoietin
- Fusion proteins
- Interferons
- Monoclonal antibodies
- Colony stimulating factors & interleukin-2

Players

- Sandoz
- Teva
- Hospira
- Mylan
- AstraZeneca
- Merck
- Pfizer
- Dr. Reddy's Lab

Biosimilars - predictions

- Globally there are 280 biosimilars in pipeline and their clinical trials are increasing at a rate of 20 - 27% annually.
- Overall world market for biosimilar mAbs will exceed $4bn by 2020

Market research 2015

TechNavio 2015

Biosimilars in US

as 10/2017

Zarxio/Sandoz, Inc. => **Neupogen**/Amgen (3/15)
Inflectra/Celltrion/Hospira => **Remicade**/Janssen (4/16)
Erelzi/Sandoz => **Enbrel**/Amgen (8/16)
Amjevita/**Amgen** => **Humira**/AbbVie (9/16)
Renflexis/Samsung => **Remicade**/**Janssen** (4/17)
Cyltezo/ **Boehringer Ingelheim** => **Humira**/AbbVie (8/17)
Mvasi/**Amgen** => **Avastin**/ **Genentech** (9/17)

FDA March 6, 2015

Zarxio (filgrastim-sndz)
the first biosimilar in US

Sandoz, Inc.'s Zarxio is biosimilar to Amgen Inc.'s Neupogen, originally licensed in 1991. Zarxio is approved for the same indications as Neupogen, as "interchangeable"

FDA 2015

FDA April 5, 2016

Inflectra (infliximab-dyyb)
second biosimilar approved by the FDA

- Inflectra is manufactured by Celltrion, Inc, for Hospira, It is biosimilar to Janssen Biotech, Inc.'s Remicade

- Multiple indications - Crohn's disease, ulcerative colitis, rheumatoid arthritis, arthritis of the spine, psoriatic arthritis & chronic severe plaque psoriasis).

FDA 2016

FDA July - 2016

Erelzi, (etanercept-szzs)

Third biosimilar approved by the FDA

- Erelzi manufactured by Sandoz Inc., is a biosimilar to Enbrel originally licensed to Amgen in 1998.

- Multiple indications - moderate to severe rheumatoid arthritis, moderate to severe polyarticular, active psoriatic arthritis, active ankylosing spondylitis and chronic moderate to severe plaque psoriasis

FDA 2016

FDA September - 2016

Amjevita (adalimumab-atto)

Fourth biosimilar approved by the FDA

- Amjevita manufactured by Amgen as a biosimilar to Humira approved in 2002 and is manufactured by AbbVie Inc.

- Multiple indications - rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis; and plaque psoriasis.

FDA 2016

Biosimilars in EU ~ 35

as 7/2017

- Omnitrope (somatropin) – EU first biosimilar approved in 2006.
- To date, **EMA has approved 38 biosimilars** - product classes of human growth hormone, granulocyte colony-stimulating factor, erythropoesis stimulating agent, insulin, follicle-stimulating hormone (FSH), parathyroid hormone and tumour necrosis factor (TNF)-inhibitor
- **Three** approvals **have been withdrawn**; two for filgrastim: Filgrastim ratiopharm in April 2011 and Biograstim in December 2016, and one for a somatropin biosimilar (Valtropin) in May 2012.
- This leaves a total of **35 biosimilars approved** for use in Europe.

World's first biosimilar mAb Infliximab
Biosimilar to J&J Ramicade

Remsima - **Celltrion Healthcare Hungary Kft.**

Inflectra - **Hospira UK Limited**

- 2013 EMEA - Infliximab has been launched in (CEE) and, as the world's first monoclonal antibody has also been approved by Health Canada. 2015 Feb launched in EU 5 (patent issues)
- The five branded anti-TNF antibodies Humira, Remicade, Enbrel, Simponi and Cimzia combined global sales $ 34.4 bln - 2014.
- Biosimilars of Humira, Remicade and Enbrel are already marketed in less regulated countries such as India and China
- The MAA of further two biosimilar TNF antibodies have been just been submitted to the EMEA

VEGF and VEGF-R Antibodies - Avastin and Lucentis Biosimilars and Biobetters

- Avastin and Lucentis first generation & Eylea and Zaltrap as the second wave of vascular endothelial growth factor VEGF antibodies plus anti-VEGF-R2 antibody Cyramzy - combined sales $13.7 bln in 2014 - cancer and eye disease indication

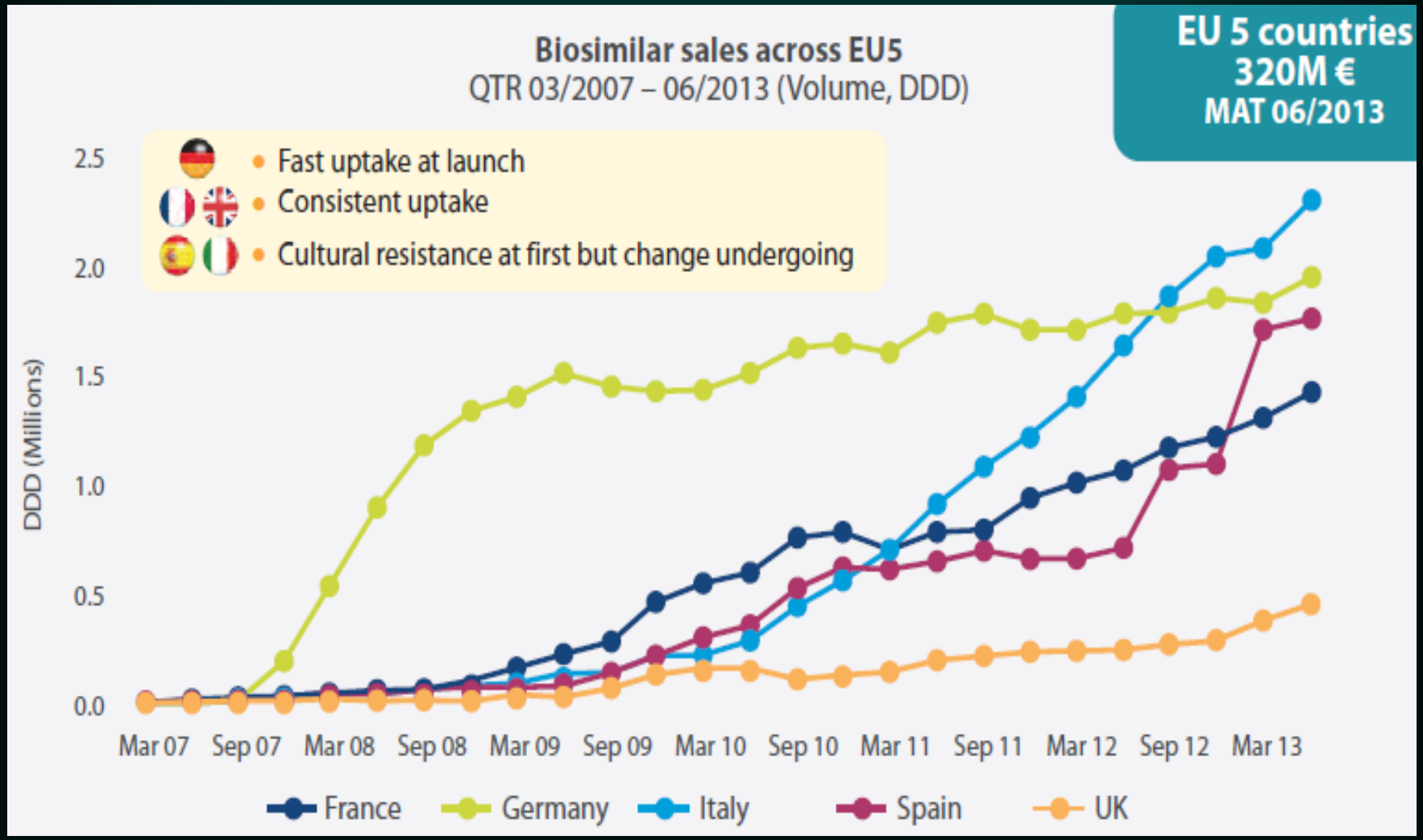
- Biobetter & biosimilar copies already in phase III trials.

IMS Health -2015

Biosimilar Challenges

- Lack of familiarity with biosimilars by physicians may hinder their use, as has been the case in Europe, where 17 biosimilars have been approved since 2006, substitutability – interchangeability could be the main issue
- Two-thirds of U.S. physician opinion leaders surveyed by Tufts CSDD would likely prescribe biosimilars, one-third would be unlikely to switch.

UPTAKE OF BIOSIMILARS IN THE EU5



Drug development trends

Regulatory Environment

A more activist FDA & EMEA working as a team may address public health threats and promote development of better healthcare products.

- Shortages of antibiotics
- Drugs for cognitive disorders
- Pediatrics
- Orphan
- Biomarker qualification
- Vaccine adjuvants
- Biosimilar interchangeability
- Vaccines - animal rules

Source: Tufts Center for the Study of Drug Development

The End