
Companies Perspective on Biosimilars

Pharma Delegate Healthcare Seminar, 1st July 2016
American Club, Tokyo, Japan

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FUJIFILM KYOWA KIRIN BIOLOGICS Co., Ltd.

Agenda

- Why Biosimilars ?
- Current Status
- Necessary Capabilities & Key Success Factors
- Future Perspective

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Why Biosimilars ?

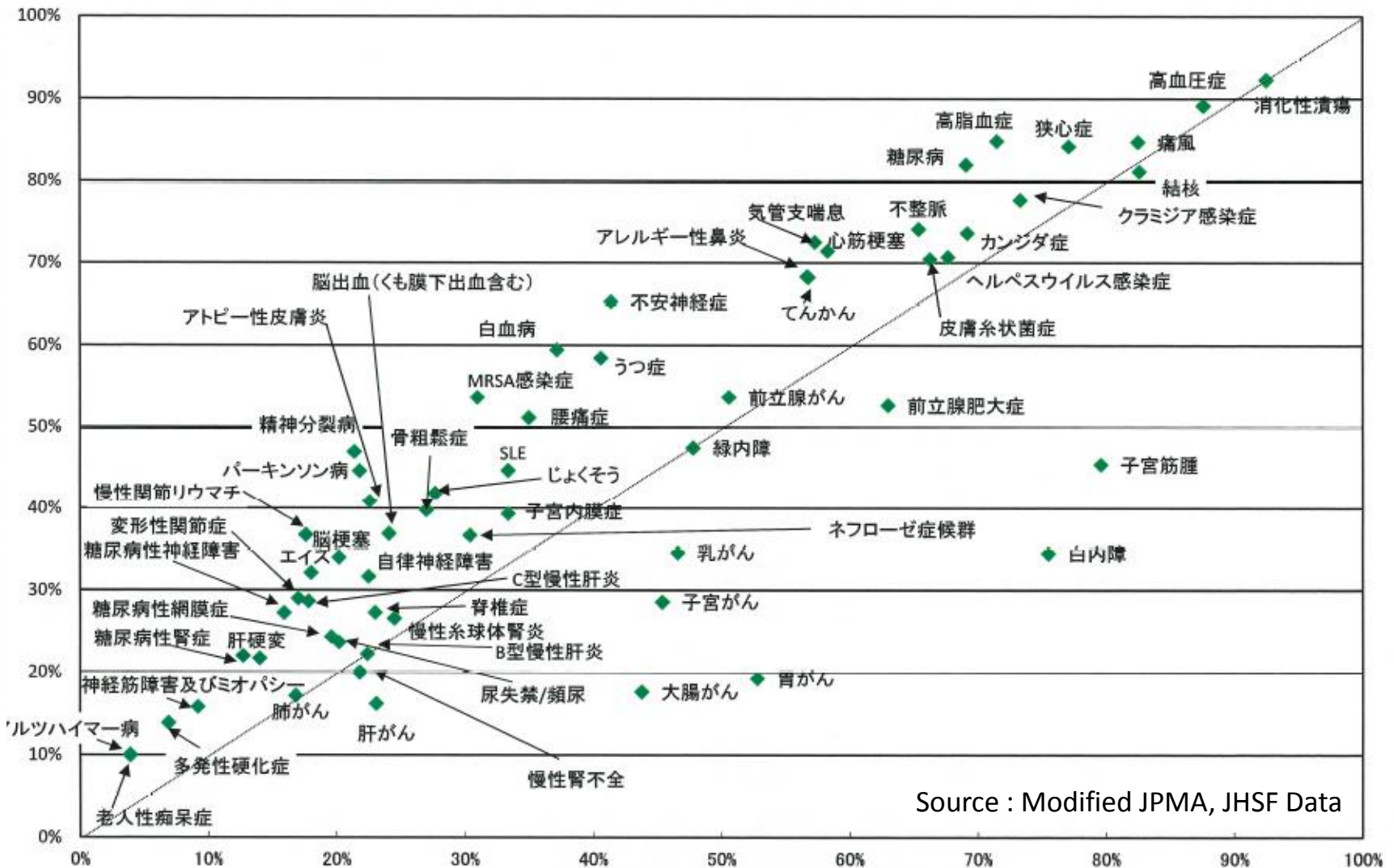
- ◆ Presence and necessity of biologics
 - Increase of biologics sales
 - Contribution of biologics to the therapy
- ◆ Economic environment to surround medical care
 - Economic depression in each country
 - Financial burden on payers (patients and government)
- ◆ Patent expiration of blockbusters
 - To expire by 2019
- ◆ Biosimilar Guidelines
 - EU from 2005, Japan in 2009, US in 2015, China in 2015

Top 20 Pharmaceuticals Sales in the World (2013-2015; US\$Bn)

Rank	2015		2014		2013	
1	Harvoni	18.1	Humira	11.8	Humira	9.9
2	Humira	15.0	Lantus	10.3	Seretide	9.2
3	Lantus	11.5	Sovaldi	9.4	Crestor	8.1
4	Enbrel	9.5	Abilify	9.3	Enbrel	7.9
5	Crestor	8.6	Enbrel	8.7	Lantus	7.9
6	Remicade	8.2	Seretide	8.7	Nexium	7.9
7	Seretide	8.0	Crestor	8.5	Abilify	7.8
8	Sovaldi	6.6	Remicade	8.1	Remicade	7.7
9	Mabthera	6.3	Nexium	7.7	Cymbalta	6.5
10	Avastin	6.2	Mabthera	6.6	Mabthera	6.3
11	Lyrica	6.0	Avastin	6.1	Avastin	5.7
12	Abilify	5.8	Lyrica	6.0	Spiriva	5.3
13	Novorapid	5.6	Herceptin	5.6	Herceptin	5.2
14	Herceptin	5.6	Spiriva	5.5	Lyrica	5.1
15	Januvia	5.4	Januvia	5.0	Copaxone	4.9
16	Spiriva	5.4	Copaxone	4.8	Januvia	4.5
17	Xarelto	5.1	Novorapid	4.7	Lucentis	4.4
18	Nexium	5.1	Nuelasta	4.6	Nuelasta	4.4
19	Copaxone	5.1	Symbicort	4.5	Glivec	4.1
20	Nuelasta	4.7	Lucentis	4.4	Atripla	4.0
Global	954.1		936.5		874.6	

Contribution of Medical Product in Each Disease Therapy (2000)

Contribution of the medicine in each disease therapy

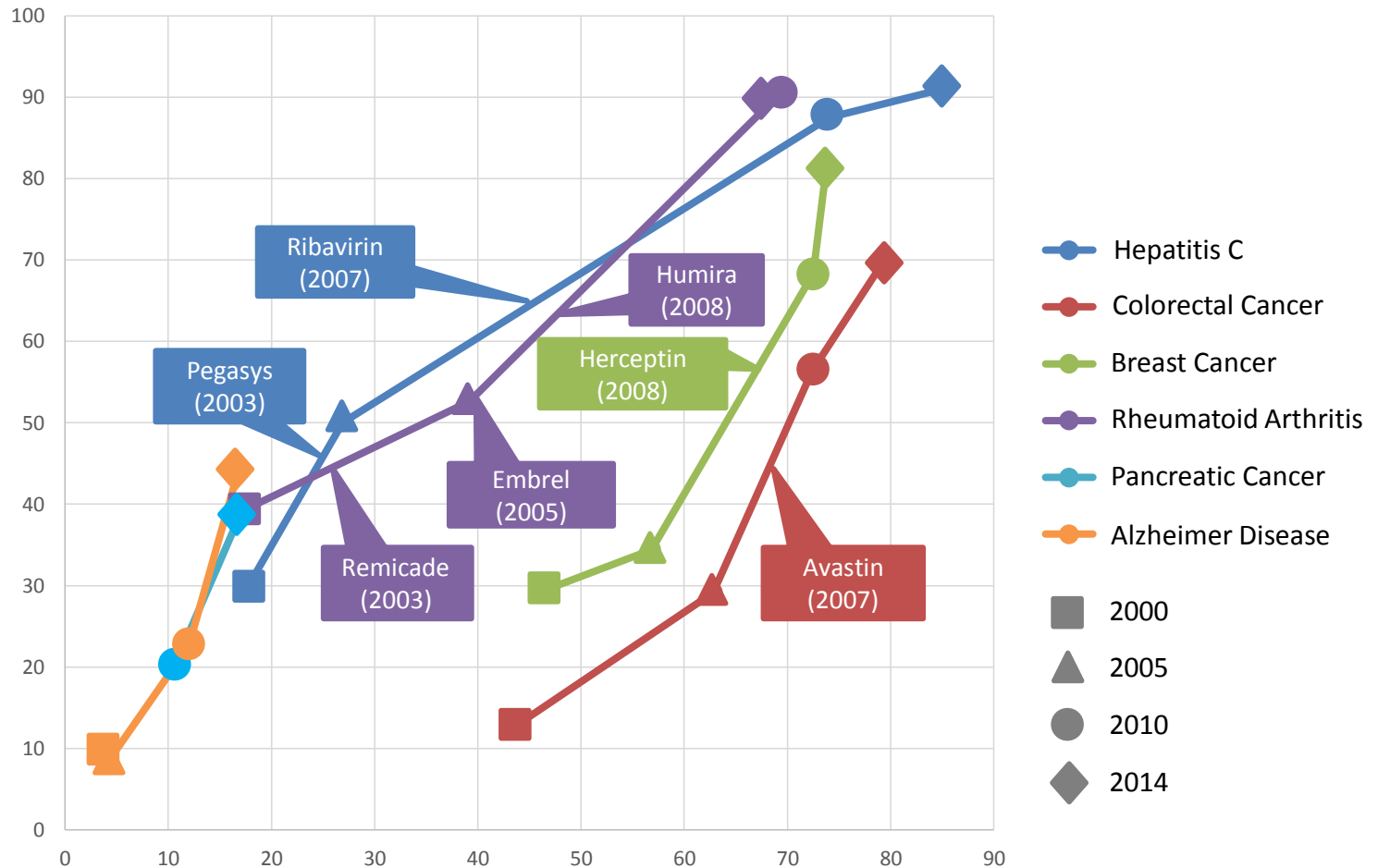


Source : Modified JPMA, JHSF Data

Satisfaction of the therapy in each disease

Contribution of Medical Product in Each Disease Therapy

Contribution of the medicine in each disease therapy



Satisfaction of the therapy in each disease

Price of Biologics (in Japan)

➤ Rituxan

- Price : 100mg 43,641 yen (US\$ 428), 500mg 213,815 yen (US\$ 2,096)
- Cost for NHL therapy
 - Rituxan cost for 8 cycles chemo therapy 2,408,776 yen (US\$ 23,615)

➤ Avastin

- Price : 100mg 41,738 yen (US\$ 409), 400mg 158,942 yen (US\$ 1,558)
- Cost for colorectal cancer therapy (10mg/kg)
 - Avastin cost for 12 cycles chemo therapy 2,909,016 yen (US\$ 28,520)

➤ Humira

- Price : 40mg 65,144 yen (US\$ 639)
- Cost for RA therapy
 - Humira cost for 1 year treatment 1,563,456 yen (US\$ 15,328)
 - (- Methotrexate cost for 1 year treatment 18,018 yen (US\$ 177))

Body weight; 60Kg, 1\$=102yen

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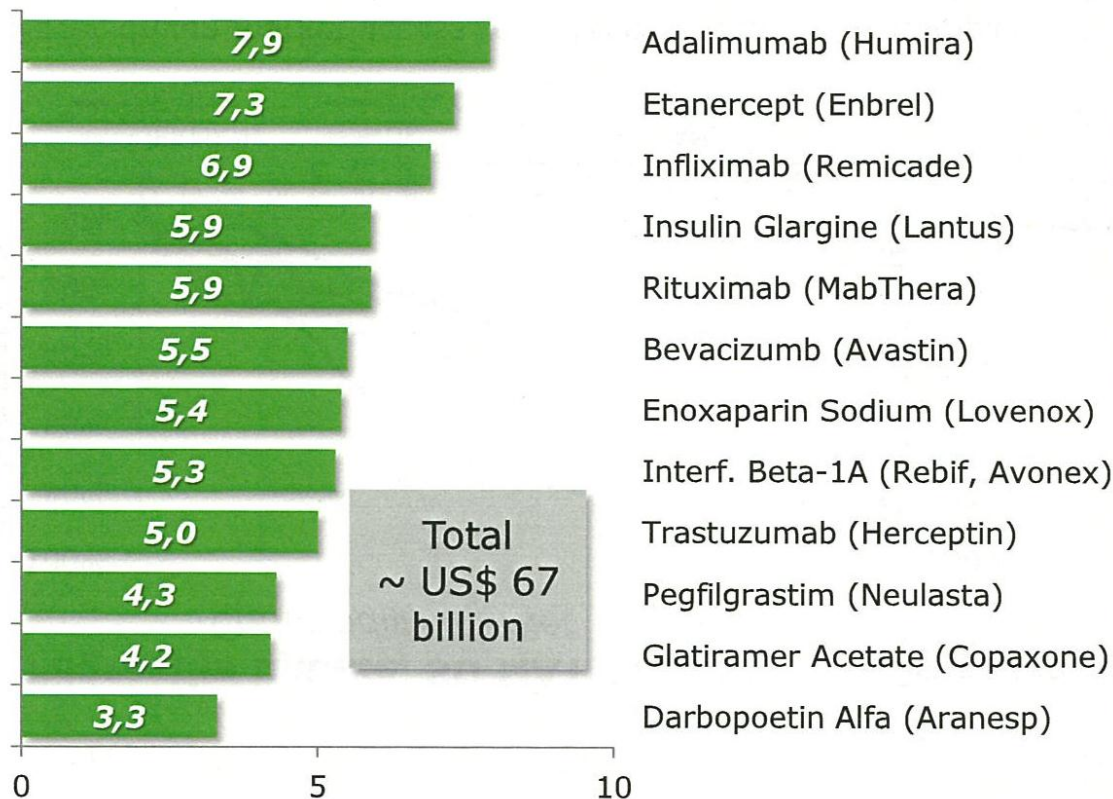
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Patent Expiry Date of Biologics

Global Sales (MAT 12/2011), US\$, Billion



EU expiry date	US expiry date
2018	2016
2015	2028 (extended)
2014	2018
2014	2014
2013	2016
2010	2017
2012	Expired
2015	2015
2014	2019
2017	2015
2015	2014
2016	2016

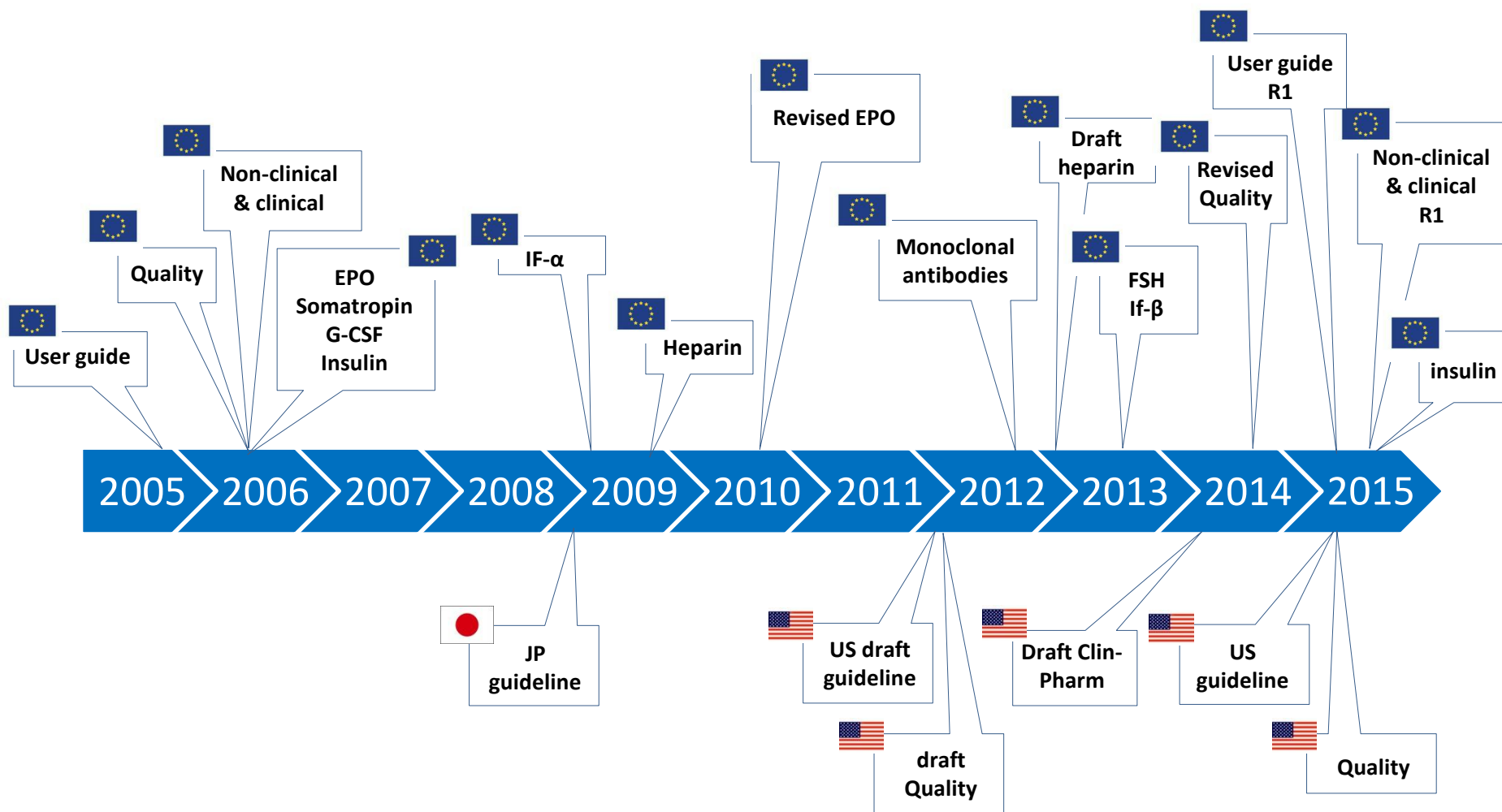
Not considered existing biosimilars such as Epoetin Alfa expired in EU, but still patent protected in US

Source : IMS Data in 10th EGA International Symposium

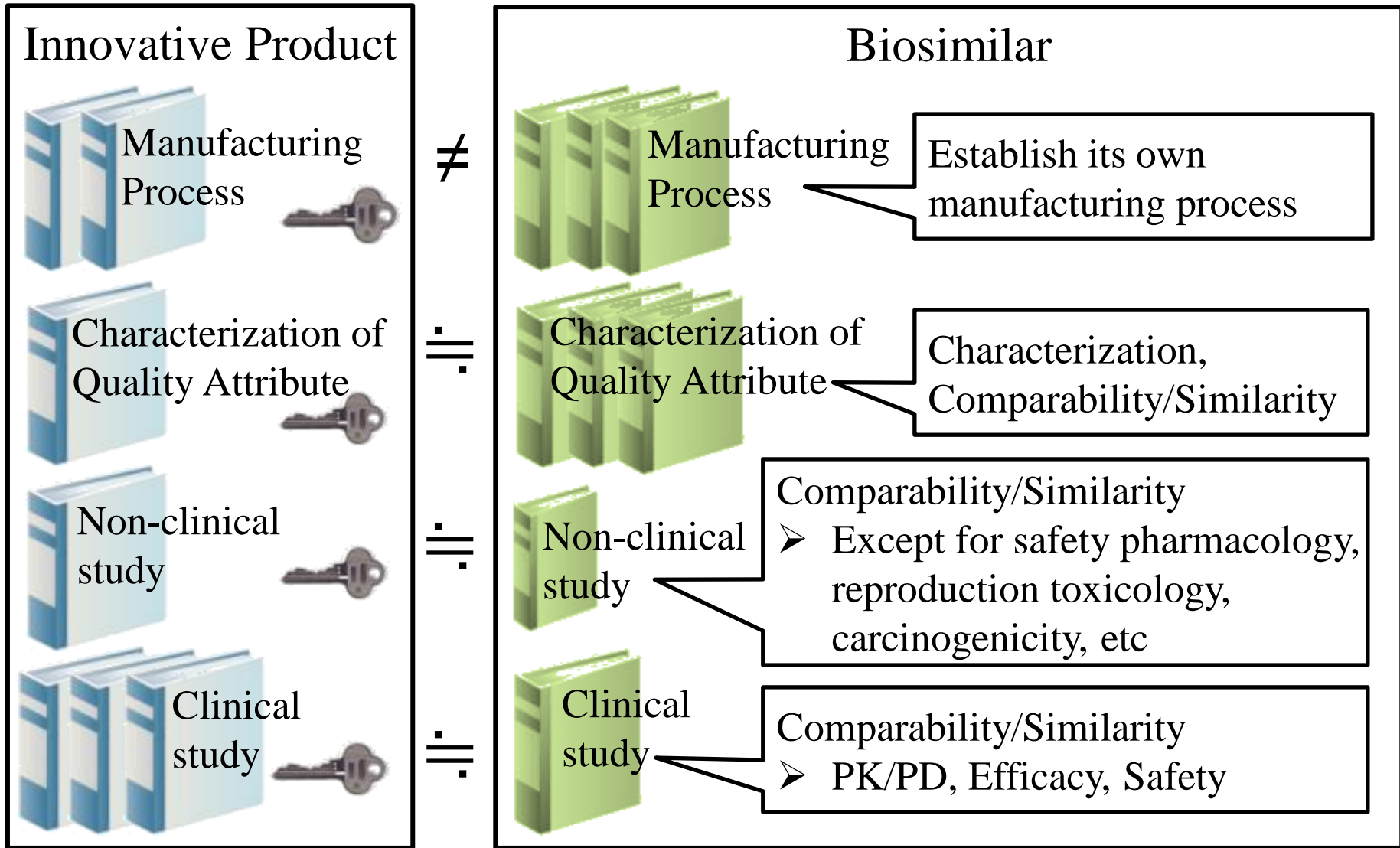
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Guideline History (EU/JP/US)



Required Data for Biosimilar Approval



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- Necessary Capabilities & Key Success Factors
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Current Status of Biosimilars

- ◆ Approved biosimilars
 - EU; somatropin(2006), epoetin(2007), filgrastim(2008), infliximab(2013)
follitropin(2013), insulin glargine(2014)
 - JPN; somatropin(2009), epoetin(2010), filgrastim(2013), infliximab(2014),insulin glargine(2014)
 - US; filgrastim(2015),infliximab(2016)

- ◆ Target molecule
 - From cytokines to monoclonal antibodies

- ◆ Players
 - Generic companies, mega pharma companies, bio-ventures
 - Alliance

- ◆ Market
 - Sales increase year by year
 - Possibility to increase the target number of patients

Approved Monoclonal Antibody Products (~2013)

INN	Trade Name	Type	Target	Approval year
Muromonab	Orthoclone OKT3	Murine IgG2a	CD3	1992
Abciximab	ReoPro	Chimeric IgG1	GP1IIa/IIIa	1993
Edrecolomab	Panorex	Murine IgG2a	EPCAM	1995
Capromab	Prostascint	Murine IgG2a	FOLH1	1996
Rituximab	Rituxan	Chimeric IgG1	CD20	1997
Basiliximab	Simulect	Chimeric IgG1	IL2R	1998
Palivizumab	Synagis	Humanized IgG1	RSV F	1998
Infliximab	Remicade	Chimeric IgG1	TNF	1998
Trastuzumab	Herceptin	Humanized IgG1	HER2	1998
Alemtuzumab	Campath	Humanized IgG1	CD52	2001
Ibritumomab tiuxetan	Zevalin	Murine IgG1	CD20	2002
Adalimumab	Humira	Human IgG1	TNF	2002
Omalizumab	Xolair	Humanized IgG1	IgE	2003
Tositumomab	Bexxar	Murine IgG2	CD20	2003
Cetuximab	Erbitux	Chimeric IgG1	EGFR	2004
Bevacizumab	Avastin	Humanized IgG1	VEGF	2004
Natalizumab	Tysabri	Humanized IgG4	α 4-integrin	2004
Tocilizumab	Actemura	Humanized IgG1	IL6R	2005
Ranibizumab	Lucentis	Humanized IgG1 Fab	VEGF	2006

INN	Trade Name	Type	Target	Approval year
Panitumumab	Vectibix	Human IgG2	EGFR	2006
Eculizumab	Soliris	Humanized IgG2/4	C5	2007
Certolizumab pegol	Cimzia	Humanized IgG1 Fab, peglated	TNF	2008
Golimumab	Simponi	Human IgG1	TNF	2009
Canakinumab	Ilaris	Human IgG1	IL1b	2009
Catumaxomab	Removab	Rat IgG2/Murine IgG2	EPCAM	2009
Ustekinumab	Stelara	Human IgG1	IL12/23	2009
Ofatumumab	Arzerra	Human IgG1	CD20	2009
Besilesomab	Scintimun	Murine IgG1	CEACAM8	2010
Denosumab	Prolia	Human IgG2	RANK-L	2010
Belimumab	Benlysta	Human IgG1	BLYS	2011
Ipilimumab	Yervoy	Human IgG1	CTLA-4	2011
Brentuximab Vedotin	Adcetris	Chimeric IgG1 conjugated with MMAE	CD30	2011
Mogamulizumab	Poteligeo	Humanized IgG1	CCR4	2012
Pertuzumab	Perjeta	Humanized IgG1	HER2	2012
Raxibacumab	Abthrax	Human IgG1	PA	2012
Trastuzumab Emtansine	Cadcyla	Humanized IgG1 conjugated with maytansionid DM1	HER2	2013
Obinutuzumab	Gazyva	Humanized IgG1	MS4A1	2013

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Blue; approved, Orange; under clinical development, Green; under pre-clinical development

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Players and Functions (mAb biosimilars)

Type	CMC Development & Manufacturing	Clinical Trial	Sales & Marketing	Products (Global Clinical Dev.)
Full Activities	Sandoz			Rituximab, Etanercept, Adalimumab
	Boehringer Ingelheim			Rituximab, Adalimumab, Bevacizumab
	Pfizer			Rituximab, Trastuzumab, Infliximab, Adalimumab
	Amgen			Trastuzumab, Adalimumab, Bevacizumab
Sales & Marketing Partner	Celltrion		Hospira	Infliximab, Trastuzumab
	Samsung		Merck	(Rituximab), Infliximab, Etanercept
Dev., Sales & Marketing Partner	(Lonza)	Teva		(Rituximab)
	Biocon	Mylan		Trastuzumab
	Momenta, Coherus	Shire (Baxalta)		Etanercept

Current Status of Biosimilars

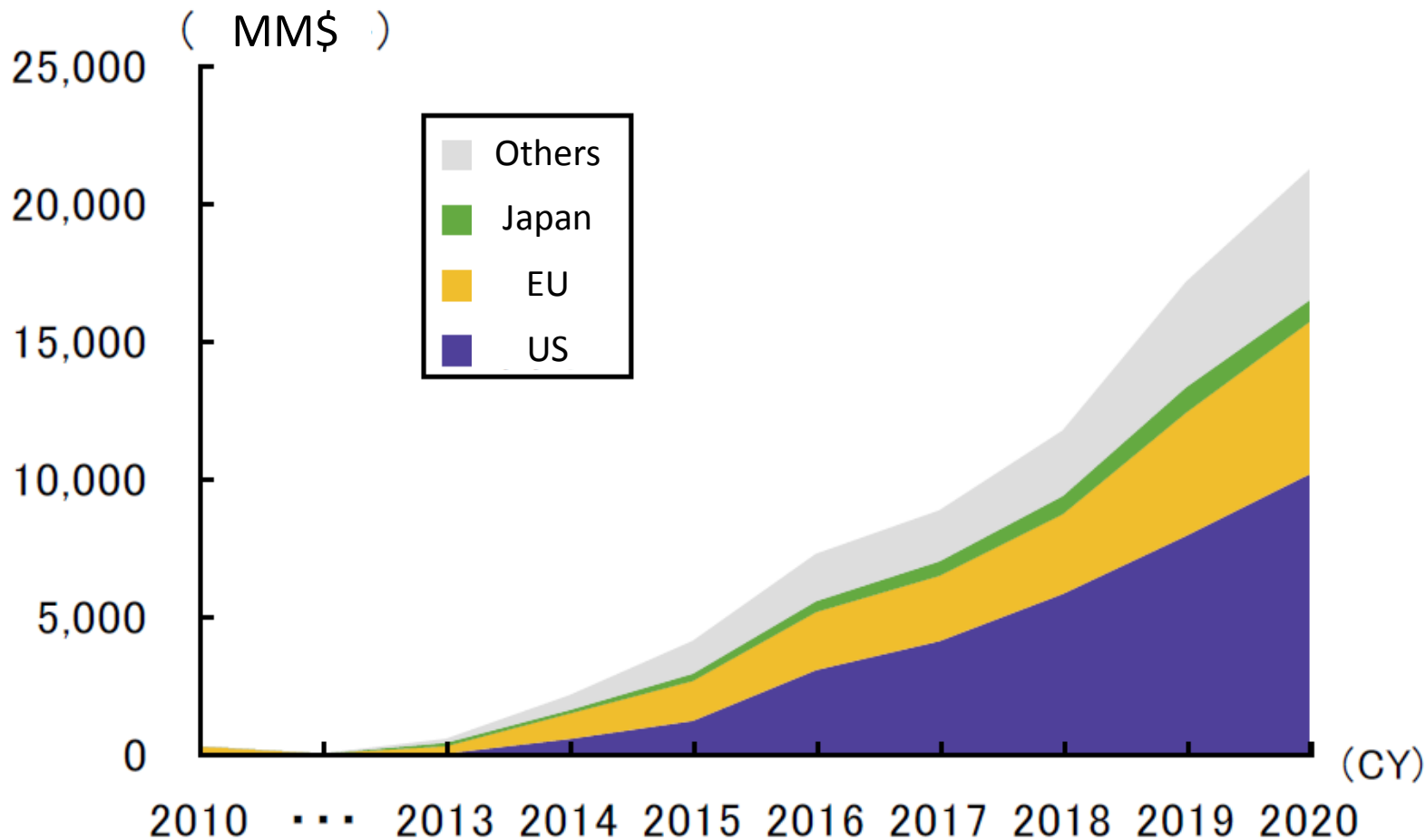
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Biosimilars Market Forecast

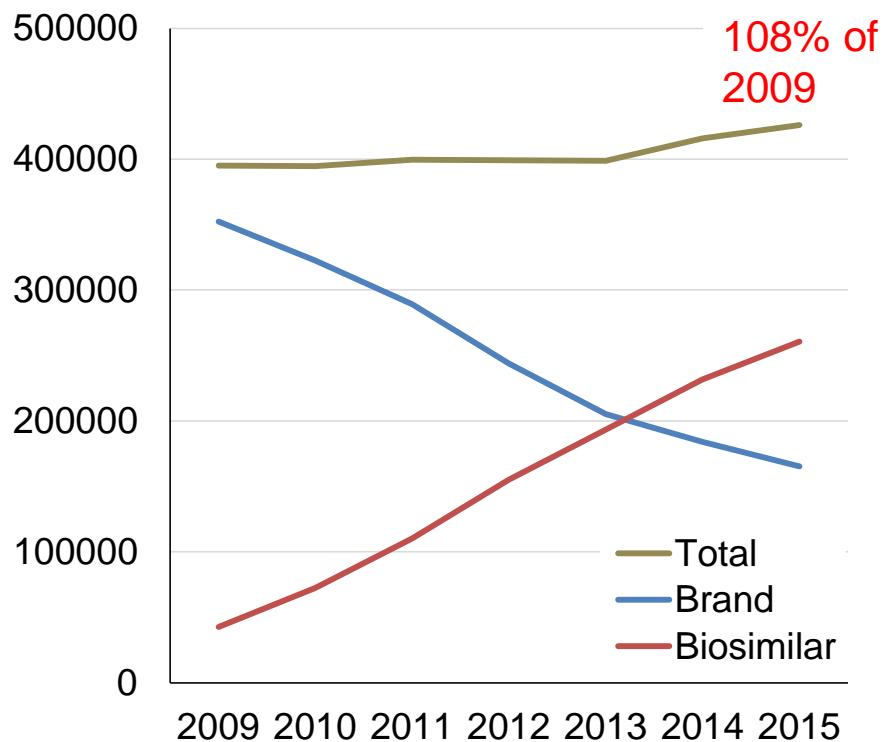


Source : IMS Shaping the biosimilars opportunity

G-CSF Market Trends in EU5 Countries

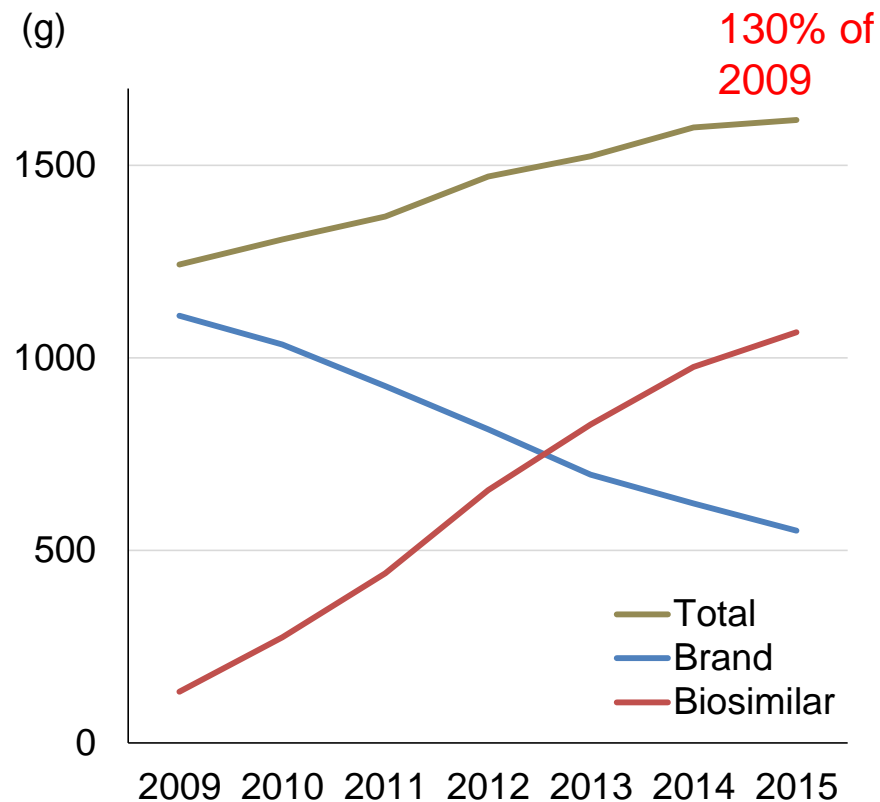
Sales Amount

[LCD/MNF (Thousands)]



Sales Volume

(g)

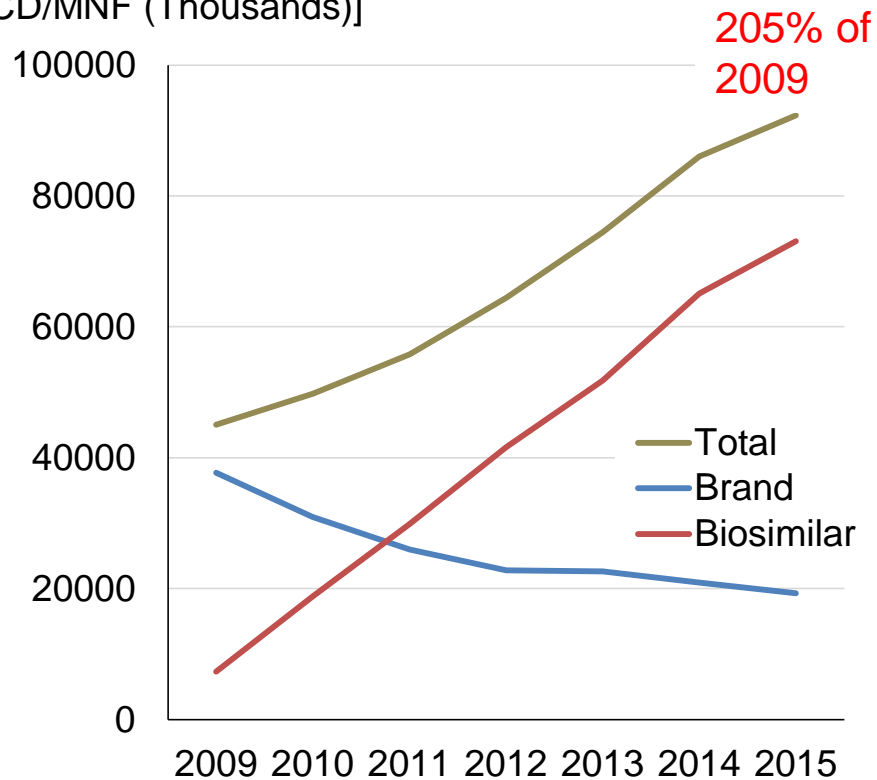


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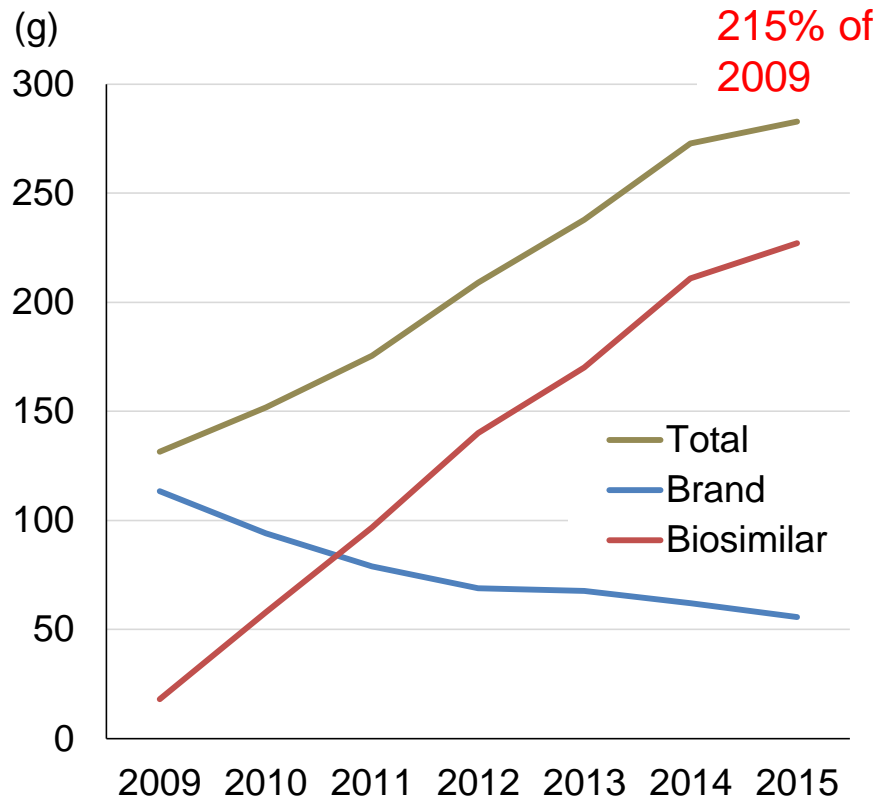
G-CSF Market Trends in UK

Sales Amount

[LCD/MNF (Thousands)]



Sales Volume



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- Future Perspective

Necessary Capabilities & Key Success

- ◆ Necessary capability to develop and market
 - From CMC development to market
- ◆ Key success factors
 - Speed, cost, and quality (similarity)

Necessary Capability to Develop and Market

CMC Development

Manufacturing

Pre-clinical Development

Clinical Development

Patent Litigation

Sales & Marketing

Financial Strength

Necessary Capability to Develop and Market

CMC Development

Manufacturing

Pre-clinical Development

Clinical Development

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CMC Development

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Pre-clinical Development

Clinical Development

Patent Litigation

Sales & Marketing

Financial Strength

Importance of CMC development

Host cell line & vector

- Same type host cell as reference product and its modification
- High expression vector system

Similarity
Titer (Cost)

Clone

- Single clone with quality and titer
- Analytical methods to select (high through put system)

Similarity
Titer (Cost)
Speed

Process

- Culture medium, resin, scale & single use bioreactor
- Conditions of culture and purification

Similarity
Titer & Yield (Cost)
Material Cost

Balance between similarity and speed/cost

Necessary Capability to Develop and Market

CMC Development

Manufacturing

Pre-clinical Development

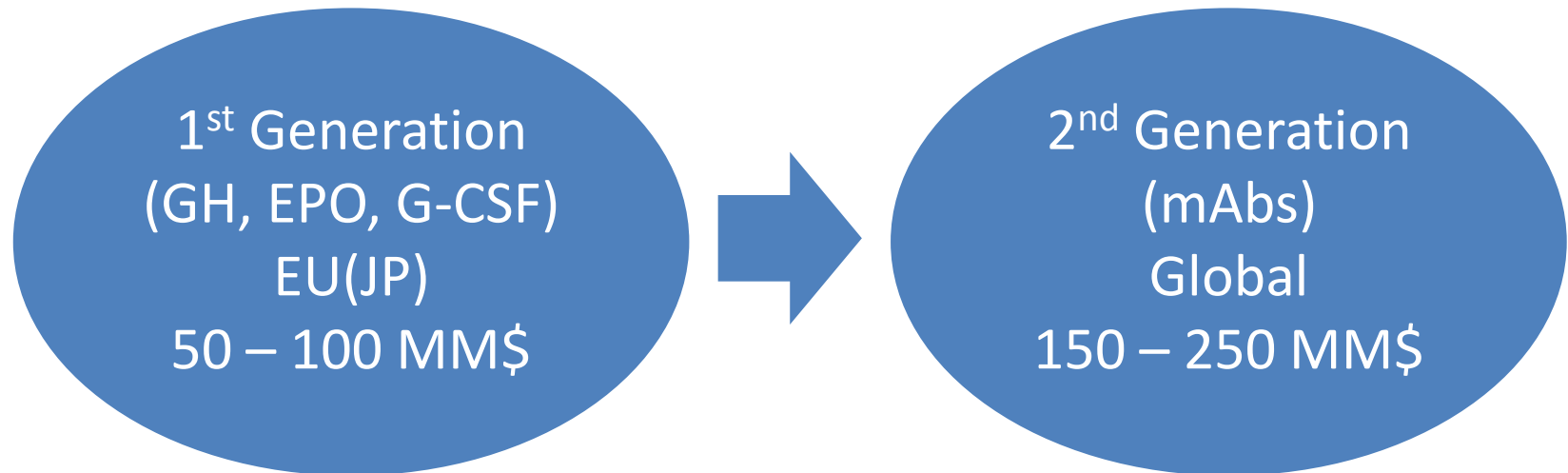
Clinical Development

Patent Litigation

Sales & Marketing

Financial Strength

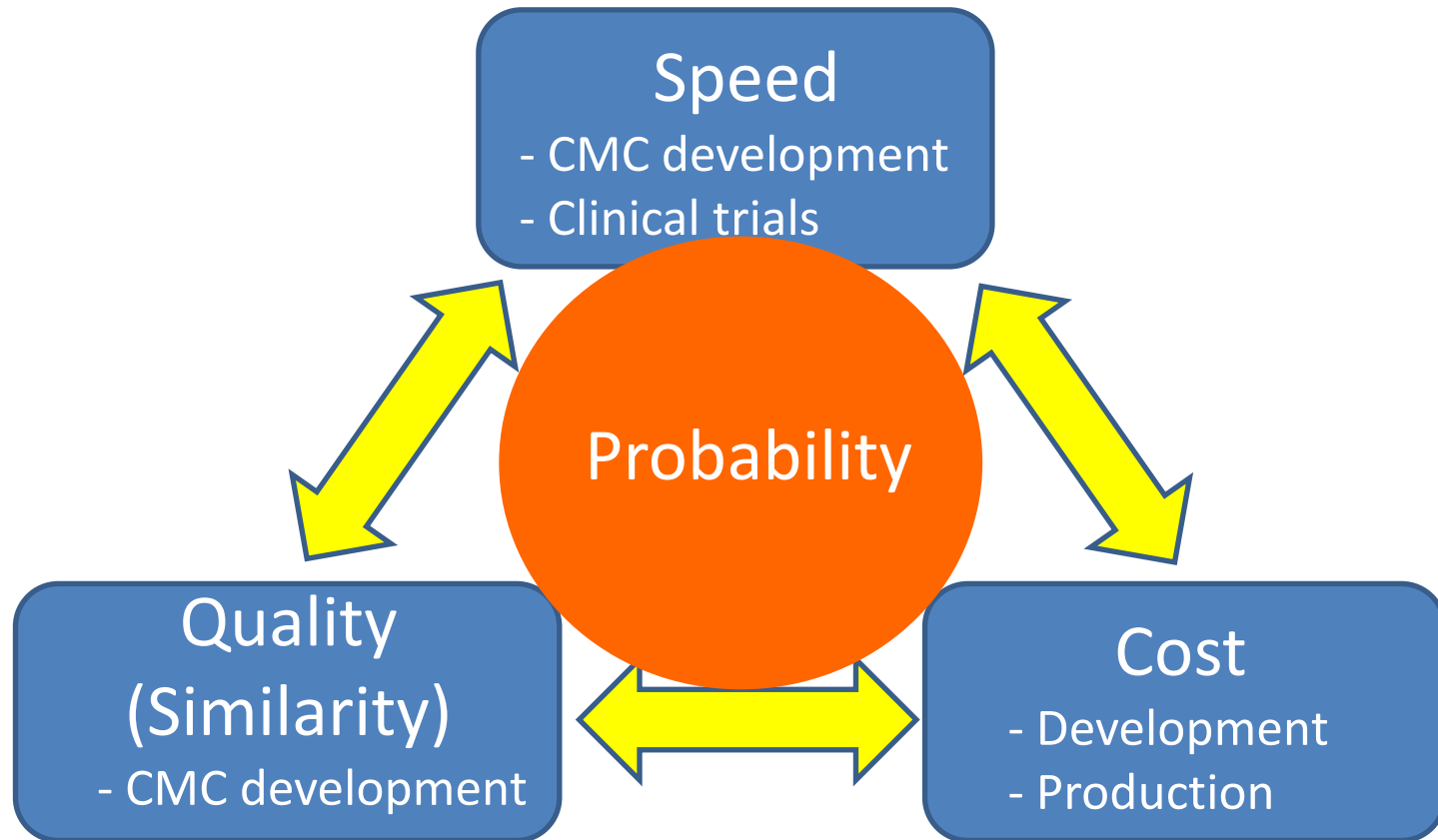
Development Cost



Necessary Capabilities & Key Success Factors

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Key Success Factors in Biosimilars Development



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Future Perspective

External Environments

- ◆ Regulation
 - Clarify & simplify
- ◆ Market Penetration
 - Appreciation by patients and HCPs
 - Payer's expectations
- ◆ Target Products
 - Hormones/Cytokines → Antibodies → New generation antibodies
 - Number ↑, market size of each product ↓

Internal Environments

- ◆ Know-how
 - Knowledge accumulation
- ◆ Cost Down
 - Development cost
 - Manufacturing cost

High-cost Medical Care Benefit System and BS (Case Study)

- Case Study
 - Under 70 years old
 - Body weight; 60kg
 - Income; 3.3~7.7 million yen
 - Remicade cost (100mg); 83,243 yen, Infliximab BS cost (100mg); 56,382 yen

Indication	Innovative or Biosimilar	Cost	Calculation of Patient payment cost	Upper limit / month	
				Normal	Multiple dose
Rheumatoid Arthritis (3~10mg/kg)	Remicade	¥ 166,486	¥ 49,945	¥ 80,100	¥ 44,000
	Infliximab BS	¥ 112,764	¥ 33,830		
Psoriasis (5mg/kg)	Remicade	¥ 249,729	¥ 74,919		
	Infliximab BS	¥ 169,146	¥ 50,744		
Crohn Disease (5~10mg/kg)	Remicade	¥ 499,458	¥ 149,838		
	Infliximab BS	¥ 338,292	¥ 101,488		

To adopt BS increases patient payment cost in the case of multiple dose

To adopt BS can reduce patient payment cost

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New Generation Antibody Products

- Fab fragment; ex) LUCENTIS®
- PEGylation; ex) CIMZIA®
- ADC; ex) ADECTRIS®, KADCYLA®
- Bispecific; ex) REMOVAB®
- Enhanced ADCC; ex) POTELIGEO®
- Others

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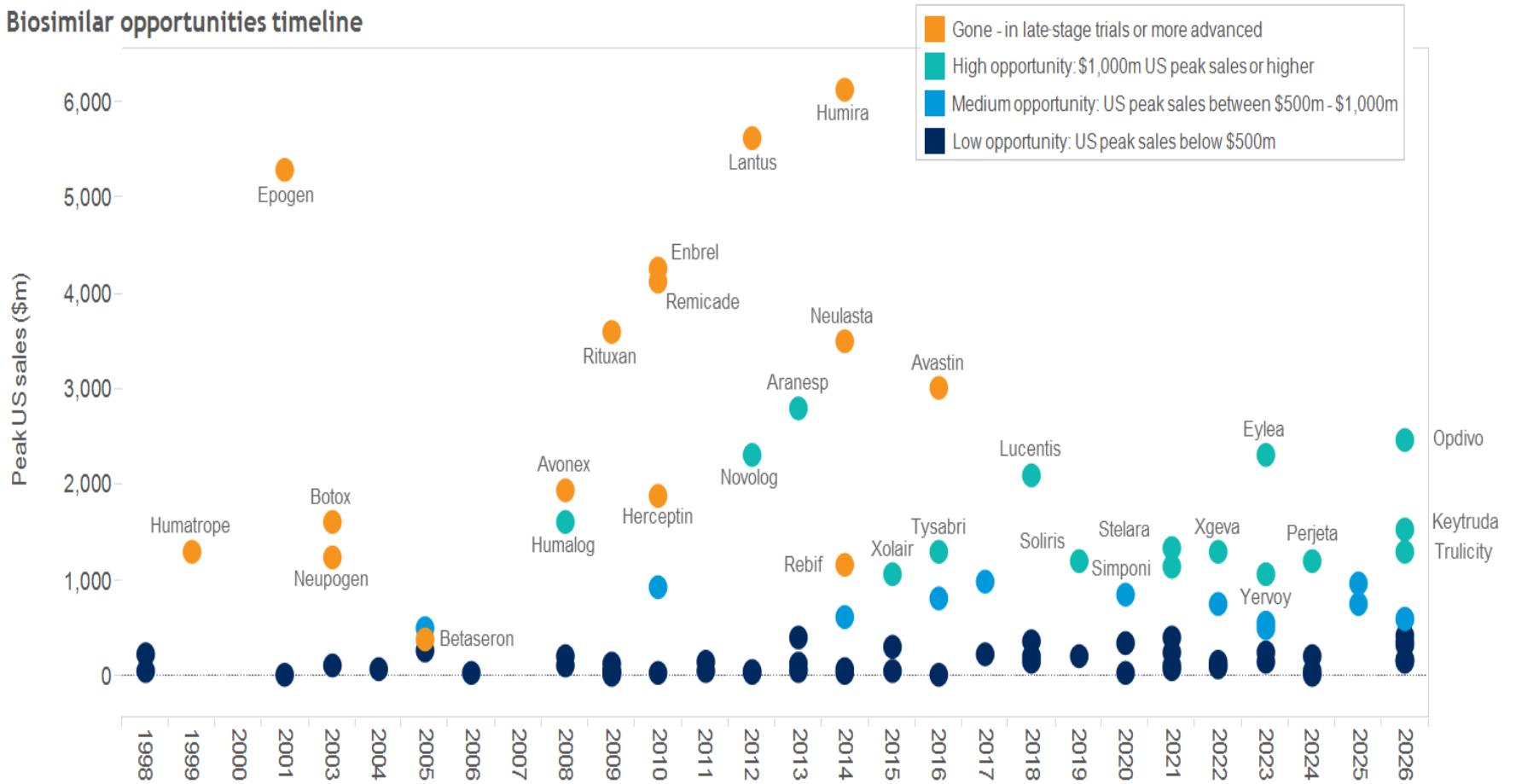
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Nivolumab	Opdivo	Human IgG4	PDCD1	2014
Pembrolizumab	Keytruda	Humanized IgG4	PDCD1	2014
Secukinumab	Cosentyx	Human IgG1	IL17a	2015
Alirocumab	Praluent	Human IgG1	PCSK9	2015
Evolocumab	Repatha	Human IgG2	PCSK9	2015
Mepolizumab	Nucala	Humanized IgG1	IL5	2015
Daratumumab	Darzalex	Human IgG1	CD38	2015
Necitumumab	Portrazza	Human IgG1	EGFR	2015
Elotuzumab	Empliciti	Humanized IgG1	SLAMF7	2015
Atezolizumab	Tecentrig	Humanized IgG1	CD274	2016

Over 500 antibody products are under clinical development





Biosimilar Opportunities Timeline

Biosimilar opportunities timeline



Future Perspective

External Environments

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Summary

- Biosimilars have attracted increasing attention
 - Blockbusters of biologics
 - Financial burden of biologics
 - Patent expiration of the blockbusters
 - Regulatory pathway (guidelines)
- Biosimilar market has expanded and has much future potential
 - Market expansion (23 B\$ in 2020)
 - Potential to increase the target number of patients
- Biosimilar development can not follow the establish generic regulatory pathway and has to follow specific biosimilar guideline
- Capabilities of CMC development, financial strength, and to solve the patent issue are especially important in biosimilar programs, and KSFs are speed, cost, and quality (similarity)
- Environment shall move to accept biosimilars, and the number of the targets for biosimilars will increase but each size of the market shall be relatively small

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