



Roche Roche Group

Observation on Follow-on Biologics / Biosimilars

CHUGAI PHARMACEUTICAL CO.,LTD.
Group Manager, External Affairs Dept.
Junichi Matsuzaki, Ph. D.

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Forward Looking Statements



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Contents

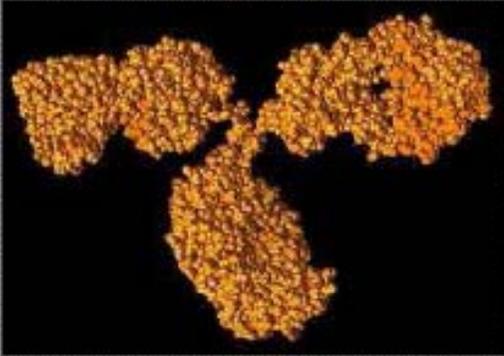
1. Features of FOBs/biosimilars
2. Guidelines on FOBs/biosimilars
3. Next steps of FOBs/biosimilars
4. FOBs/biosimilars of antibody drugs

Follow-on Biologics (FOBs)/Biosimilars



- ◆ Biological products made by manufacturers other than the originator and developed as similar products referring to the original product after its patent expiration.
- ◆ From a scientific view, FOBs/biosimilars are not “identical” or “same” with the original product, therefore different processes and requirements compared to general generic drug development are required.
- ◆ Two processes for development are possible;
 - ✓ New drug application with a full data package as same as the original bio-product. (The Japanese guideline does not define this case as a FOB)
 - ✓ Application with comparable data to the original product in quality, safety and efficacy based on comparative studies. (Expectation of reduction of development costs and time)

Complexity of Drugs by Molecular Size

	Small Molecule	Protein	Large Protein
Size	<p>Aspirin 21 atoms</p> 	<p>hGH ~ 3000 atoms</p> 	<p>IgG Antibody ~ 25,000 atoms</p> 
Complexity	<p>Bike ~ 20 lbs</p> 	<p>Car ~ 3000 lbs</p> 	<p>Business Jet ~ 30,000 lbs (without fuel)</p>  <p>Source: adapted from Genentech</p>

How many/much checks/times/labors are needed to keep the functions?

Definition of Wording

FOBs are different substances from the original product !

Generics

Biosimilars: Similar Biological Medical Products

FOBs : Follow-on biologics

SBPs : Similar biotherapeutic products

SEBs : Subsequent entry biologics

Sameness [identical] => Not applied for biosimilars

Similarity =>Applicable for evaluation of biosimilars

Comparability =>ICH-Q5E (minor process change by the same manufacturer,

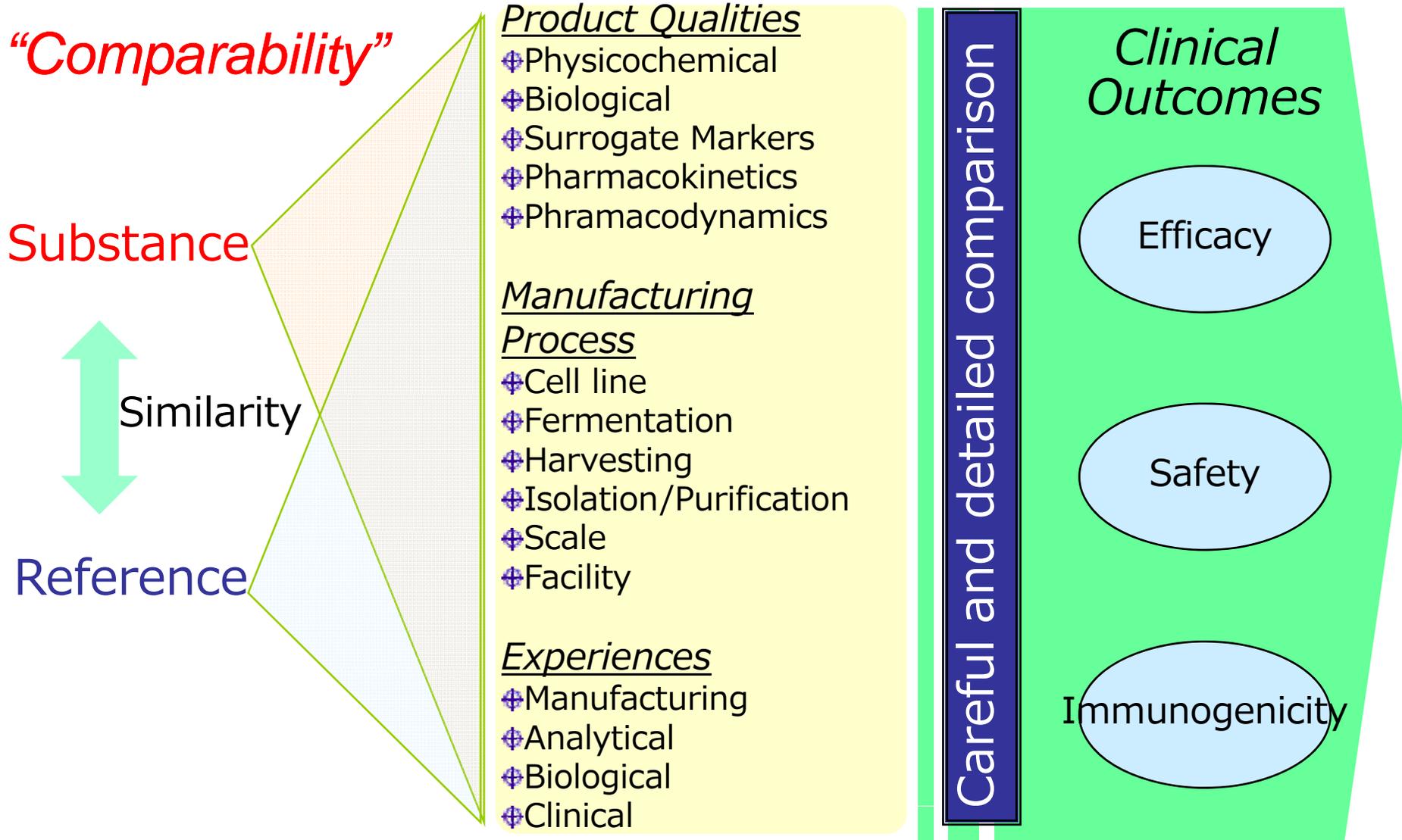
(The Japanese guideline is on extension of this concept)

Hurdles for 'Biosimilars'

- Production capabilities including facilities, technology and human resources
 - Complicated and unclear patent situation; expensive royalties
 - Difficulties in assessment and proof of comparability, including safety
 - Unforeseeable direction of regulatory authorities
-
- Complex nature of materials (heterogeneity, impurities, high-ordered structure, etc.)
 - Insufficient scientific methodology for assessment of chemical/biological comparability
 - Many parts of the methodology rely on product-by-product experience
 - Proof of comparability requires an enormous amount of data (manufacturing process/site change by original manufacturer)
 - Generic manufacturers do not have access to full data of brand products
 - Impossible to predict safety (especially immunogenicity)

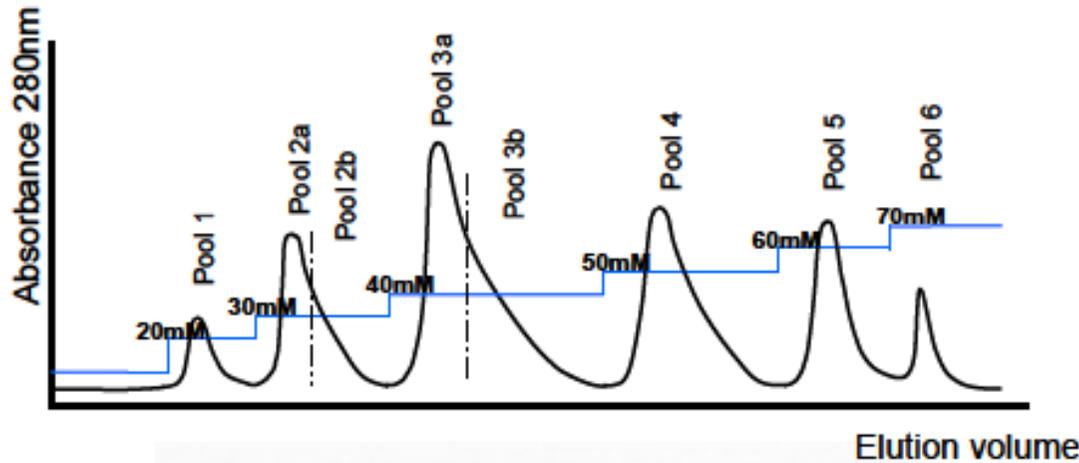
Abbreviated approval process does not have sufficient scientific support
in the case of 'FOBs' → Independent process for 'FOBs'

Grounds for Comparability of Biologics

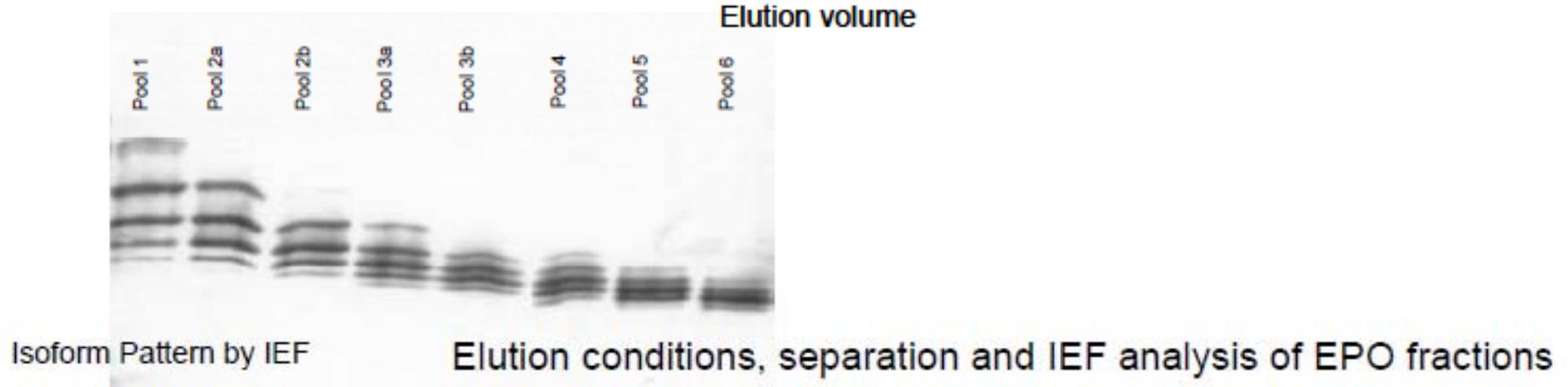


Only part of “Properties” available to FOB/biosimilar makers

Heterogeneities of Bioproducts (EPO)



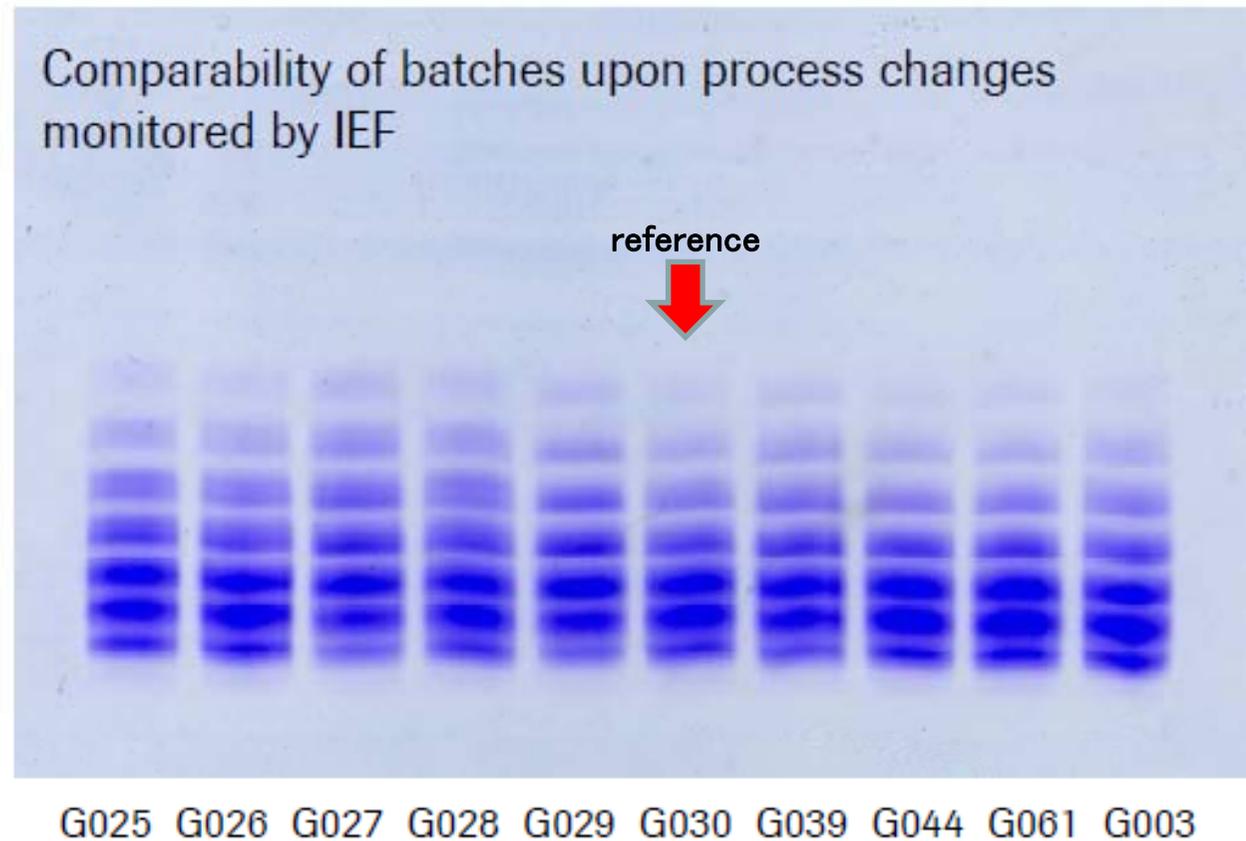
- Process conditions and in-process controls will determine the product composition



(Dr. Stephan Fischer, Roche Penzberg)

Comparability of the Product Batches

From an established process
(part of “comparability” data)



G025-G029: 5 fermentation runs (basic process)

G030: reference standard

G039: variation, optimized RP-HPLC

G044: variation, sterile filtration

G061: variation, fermentation media constituent

G003: variation, produced in new building

Source: H: Haug, V. Pfeifer, Roche Penzberg

Difference of Product Profile

Product from different manufacturers

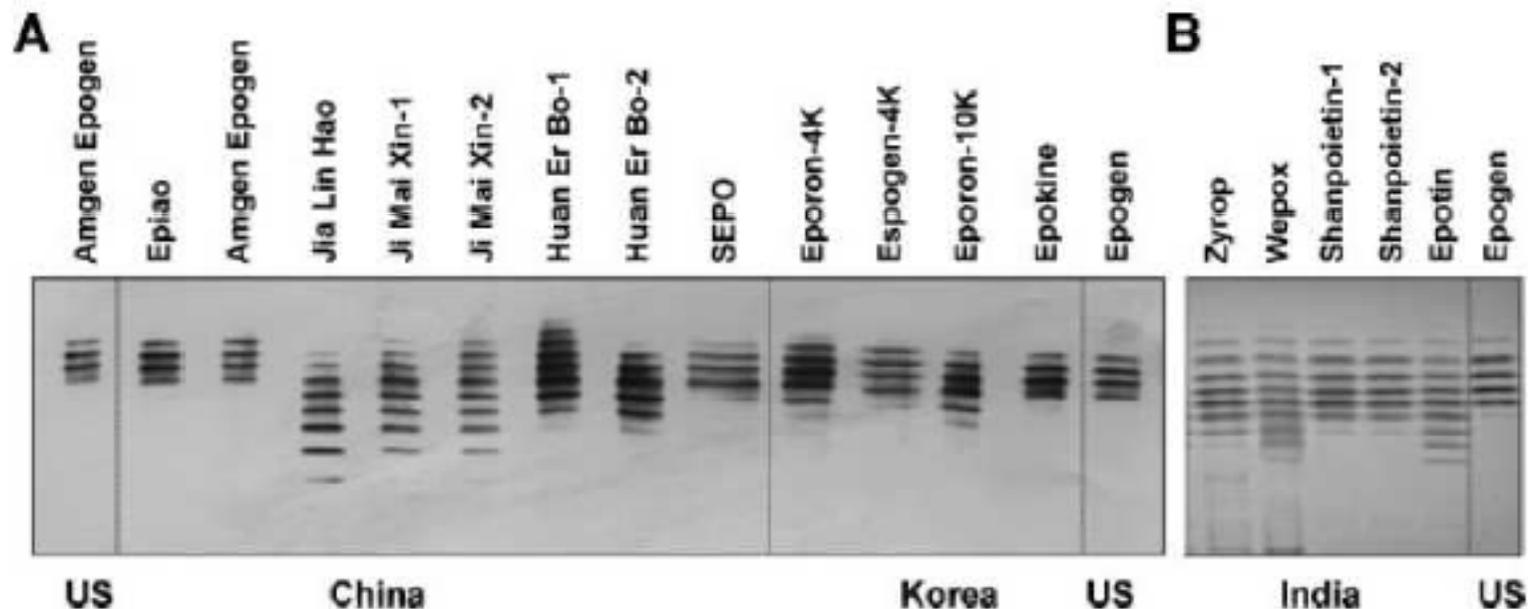
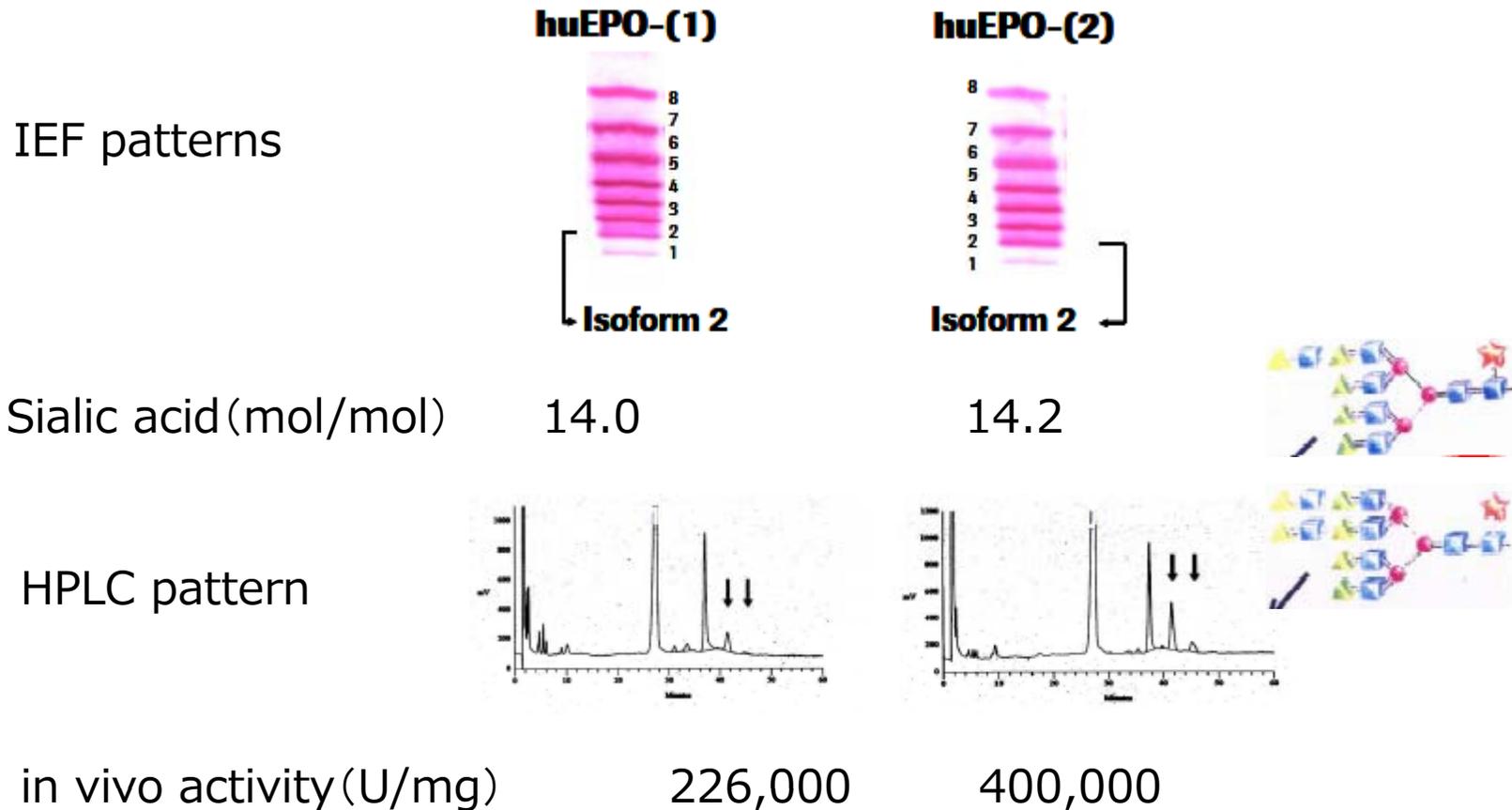


Figure 1. Iso-electro-focus (IEF) Gel with Western blots for isoform detection: (A) samples from China (lanes 2–9) and Korea (lanes 10–13) and (B) samples from India (lanes 1–5).

Park et al., J Pharm Sci Sep 2008, <http://dx.doi.org/10.1002/jps.21546>

Note: Products above are not approved according guidelines of EU/Japan

Microheterogeneity Affects to Bioactivity



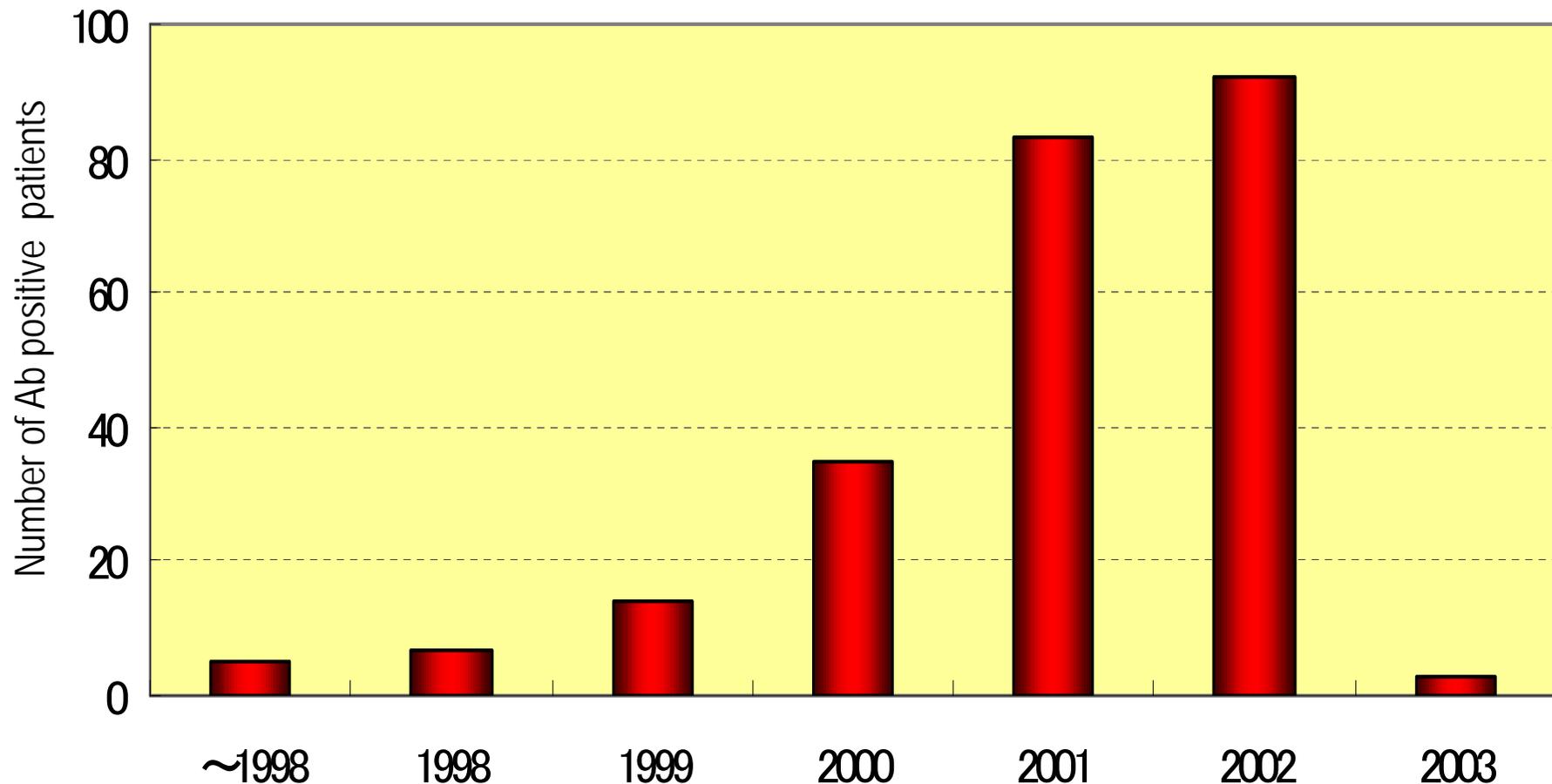
Available assays are insufficient to prove identity.
 Microheterogeneity changes biological activity of the product.

(Dr. Stephan Fischer, Roche Penzberg)

Anti-EPO Ab by EPREX Administration



Even in the case of site-change by the same manufacturer according the regulations, an unexpected event happened.

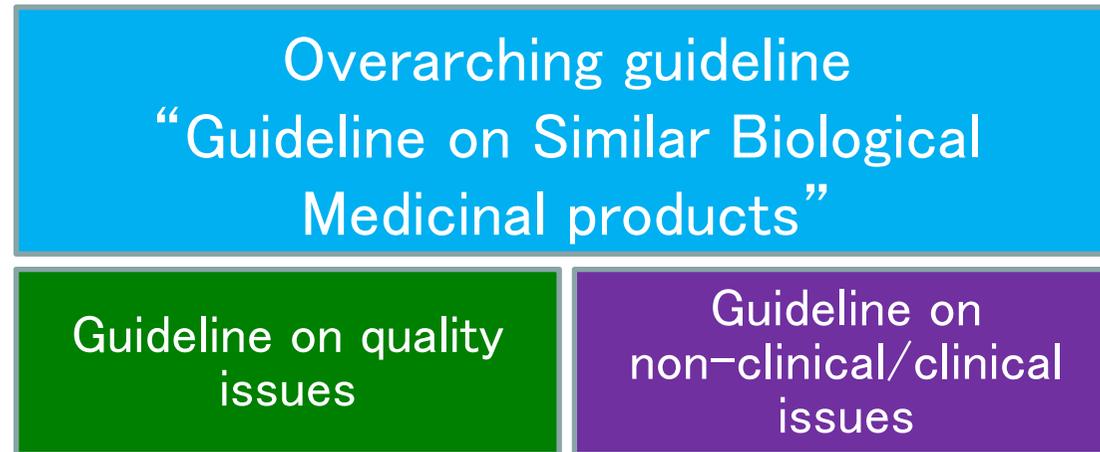


Contents

1. Features of FOBs/biosimilars
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Guidelines of Biosimilars in EU

Current



Product-class Specific Annexes (non-clinical/clinical)

Insulin

hGH

G-CSF

EPO

in preparation

IFN- α
LMWH

Next issues

Pharmacovigilance, Revision of EPO guideline
Immunogenicity, Biosimilars of antibody drugs

Approved Biosimilars in EU

Brand name	Generic name	Company	Approval
Omnitrope®	Somatropin	Sandoz	Apr, 2006
Valtropin®	Somatropin	BioPartners	Apr, 2006
Binocrit®	epoetin alfa	Sandoz	Aug, 2007
Epoietin alfa-Hexal®	epoetin alfa	Hexal	Aug, 2007
Absamead®	epoetin alfa	Medice Arzneimittel	Aug, 2007
Silapo®	epoetin zeta	Stada Arzneimittel	Dec, 2007
Retacrit®	epoetin zeta	Hospira Enterprises	Dec, 2007
Tevagrastim®	filgrastim	Teva Generics	Sep, 2008
Ratiograstim®	filgrastim	Ratiopharm	Sep, 2008
Biograstim®	filgrastim	CT Arzneimittel	Sep, 2008
Filgrastim ratiopham®	filgrastim	Ratiopharm	Sep, 2008
Filgrastim Hecal®	filgrastim	Hexal	Feb, 2009
Zarzio®	filgrastim	Sandoz	Feb, 2009

(Insulin Marvel: withdrawal, Alpheon (IFN-a): rejection)

Guideline on FOBs in Japan

March 4, 2009

- ◆ Guideline to secure quality, safety and efficacy of follow-on biologics
- ◆ Generic and brand names of follow-on biologics
- ◆ Application for approval of follow-on biologics
- ◆ MHLW's comments for the public opinions on the guideline draft

July 21, 2009

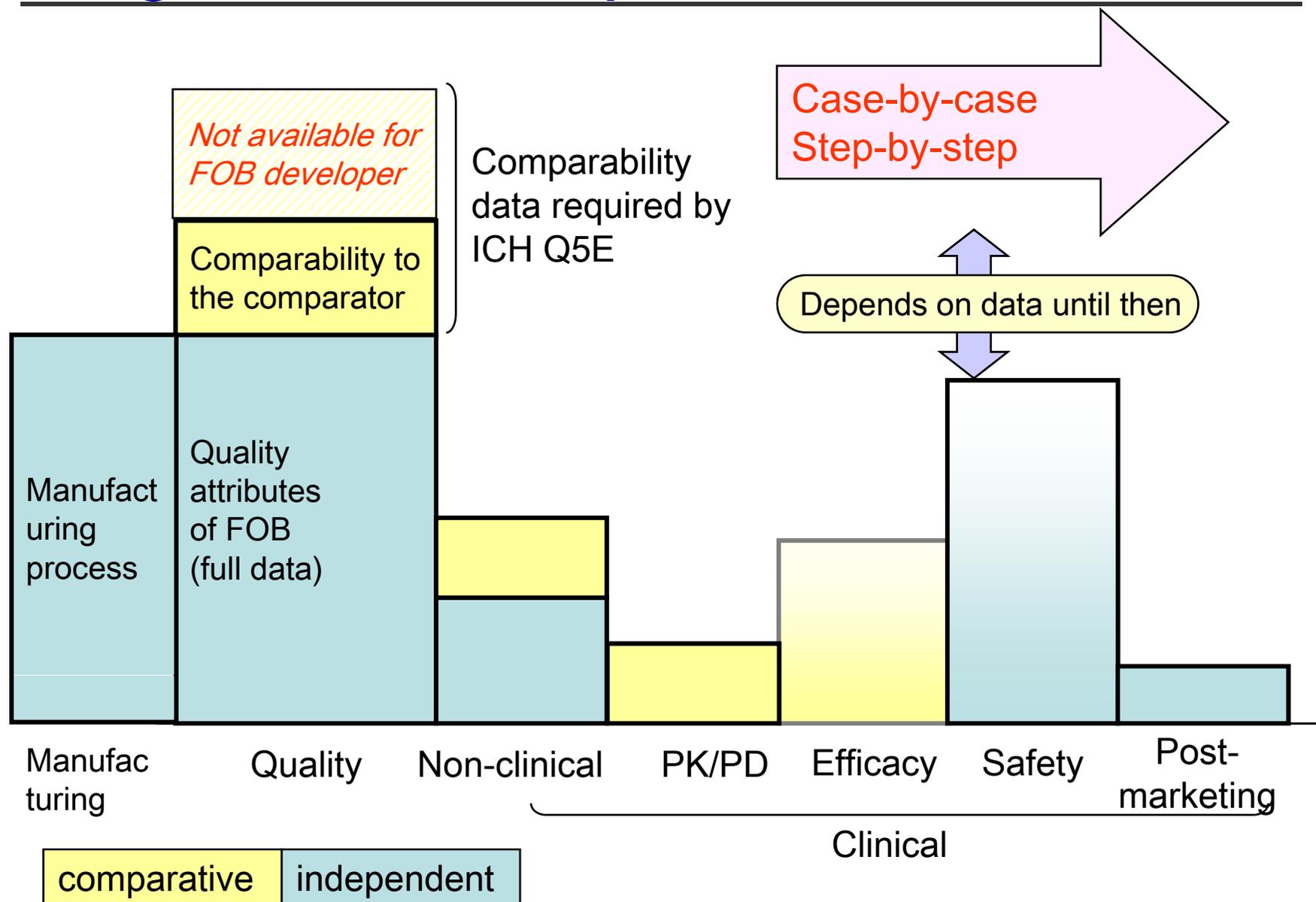
- ◆ Questions and Answers regarding the guideline

Major Features of Japanese/EU GL

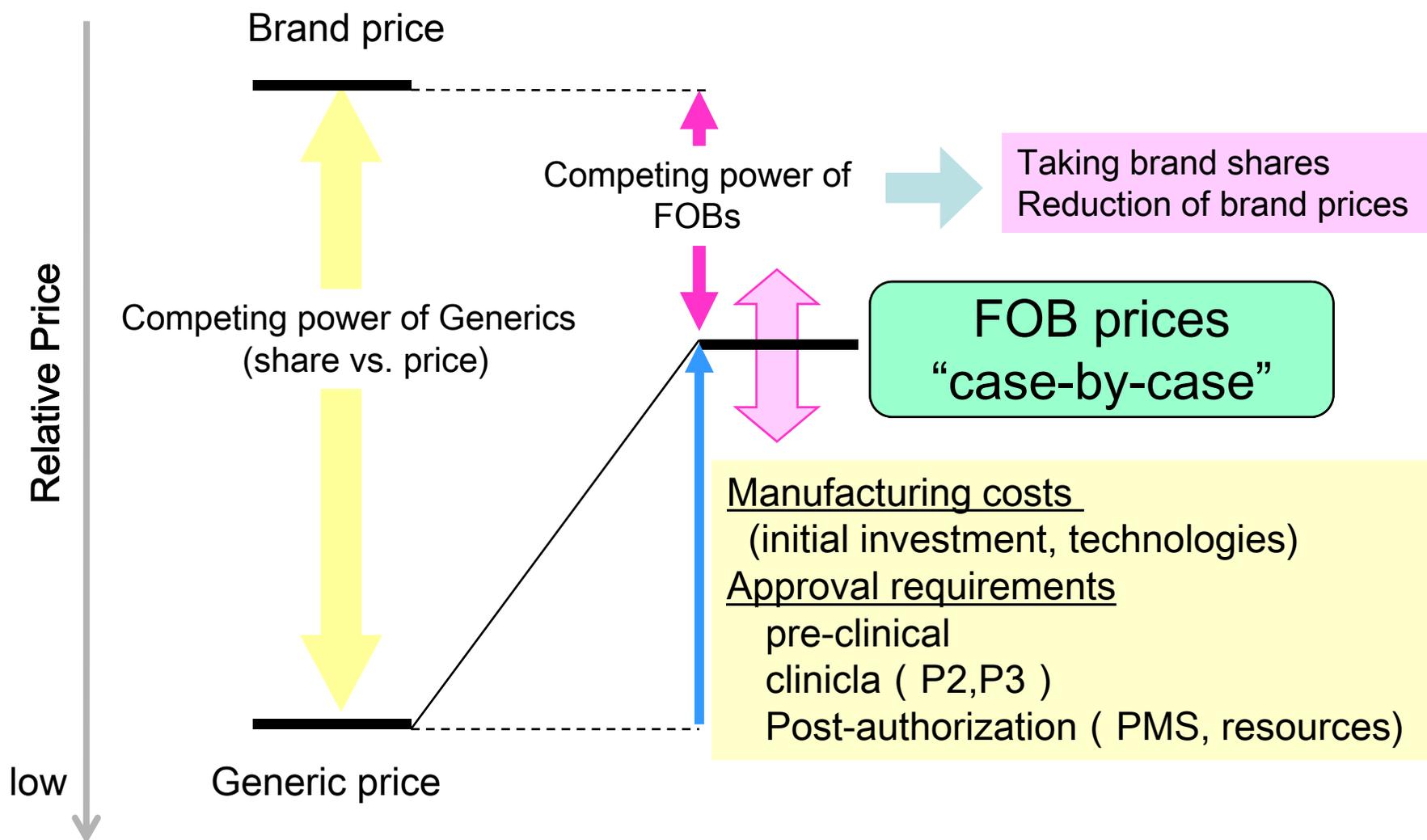


	Japan	EU
Framework	Single guideline covering all protein drugs (insulin to Mab)	An overarching GL and sub-GLs by product
Basic concept	Evaluation by comparability studies on quality (ICH Q5E) and PK/PD profiles, together with clinical data complementing the data (case-by-case and step-by-step approach)	Proof of “ similarity ” in combination of quality, non-clinical and clinical study data based on comparative studies
Post approval	Plans for post-marketing surveillance study and risk management required at submission of application	
Naming	Nonproprietary and brand names for FOBs should be distinguished from the comparator or other FOBs	INN: same as the comparator

Image of Data Requirements



Price Competition of FOBs



(Biosimilar prices are 10~40% off to brand prices in EU)

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Situation in the USA (1)

Review for drug approval in the USA

Food Drug and Cosmetic Act

Traditional chemicals, Hormones (Insulin, hGH, etc.)

=>NDA 505 (b) 1 New drugs (full data)

=>NDA 505 (b) 2 New drugs (published data usable)*

=>ANDA 505 (j) Generic drugs (abbreviated review)

Public Health Service Act

Biological products (cytokines, antibodies, and others)

=>BLA New drugs (full data)

Need of a new law for abbreviated review process of
FOBs

(*Omnitrope was approved but FDA does not recognize it as a FOB)

Situation in the USA (2)

	Interchangeability	Biosimilar exclusivity	Brand exclusivity
Access to Life Saving Medicines Act (Feb 07)	yes	180 days	none
Patient Protection & Innovative Biologic Medicine Act (Apr 07)	no	none	12 years
Biologics Price Competition & Innovation Act (June 07)	yes	1 year	12 years
Pathway for Biosimilars Act (March 08)	yes	2 years	12-14 years
Promoting Innovation & Access to Life-saving Medicines Act (March 09)	yes	180 days	5 years
Affordable Health Choice Act (July 09)	yes	1 year	12 years



Entry of FOBs into the US Market

Anticipated Biosimilar Entry Dates for Selected Biologic Brands			
Biologic Class	Branded Biologic	USA	Europe
		Biosimilar Entry	Biosimilar Entry
hGH	Genotropin, Humatrope	2006	2006
ESA	Epogen, Procrit/Eprex	2013	2007
	Aranesp	post-2015	post-2015
G-CSF	Neupogen	2013	2009
	Neulasta	2015	2013
Insulin	Humalog	2013	2013
	Lantus	2015	2014
	Levemir	2019	2014
TNF-alpha inhibitor	Enbrel	2014	2014
	Remicade	NE	NE
	Humira	2016	2018
Interferon beta	Betaseron/Betaferon	2014	2015
	Avonex	2014	2015
	Rebif	2014	2015
MAb (oncology)	Rituxan/MabThera	2015	2013
	Erbitux	post-2015	2014
	Herceptin	post-2017	2013

Notes: a = Sandoz filed Omnitrope via the 505(b)(2) pathway in the United States; an abbreviated BLA pathway (ABLA, "biosimilars pathway") will not be available until 2010. Date reflects the launch of agents filed via an ABLA pathway. hGH = human growth hormone, ESP = erythropoiesis stimulating protein, G-CSF = granulocyte colony stimulating factor, TNF = tumor necrosis factor, MAb = monoclonal antibody, NE = None expected.

© Decision Resources, Inc., 2009
Source: Decision Resources, Inc.

- ◆ Patent expiration of major bioproducts starts in 2013
- ◆ Abbreviated BLA (ABLA) will be established after 2010
(Decision Resource, 2009)

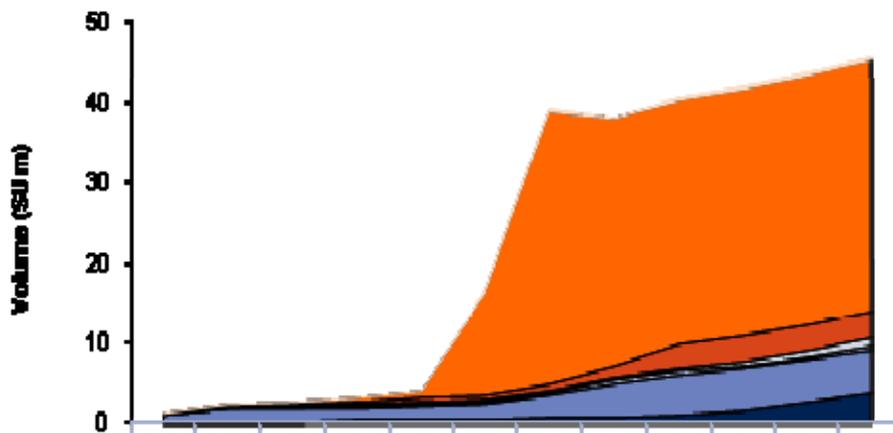
- ◆ Biologics in the US prescription drug market amount for 45 billion USD in 2008年
- ◆ 25% of new drugs are biologics
(Washington Post, July 2009)

- ◆ Patent expirations of the 27 top biologics* will happen soon after 2015
- ◆ Global bio-market totals 112 billion USA. The top 27 products account for 87% share
(FTC report, June 2009)

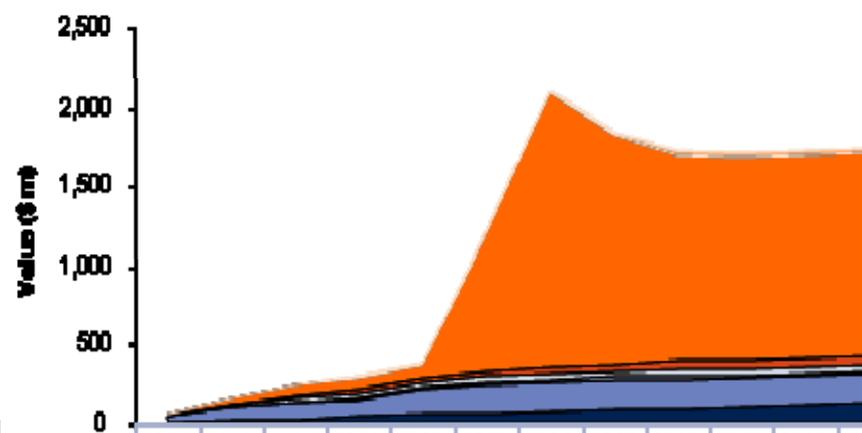
*27 top biologics: Avastin, Enbrel, Remicade, Humira, Rituxan, Herceptin, Lantus, Epogen/Procrit, Neulasta, Novolog, Erbitux, Aranesp, Recombinate, Lucentis, Avonex, Novolin, Humalog, Pegasys, Rebif, Crezyme, Tysabri, NovoSeven, Synagis, Neupogen, Betaseron, Humulin Kognate FS

Market Growth of FOBs

The biosimilars market, seven major markets, 2008–19



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Japan	-	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.2	0.3	0.4	0.5
US	0.1	0.2	0.5	0.8	0.8	13.1	34.3	31.0	30.5	30.8	31.0	31.3
UK	0.0	0.1	0.2	0.4	0.8	0.8	0.8	1.4	3.0	3.4	3.4	3.5
Spain	0.0	0.1	0.1	0.2	0.4	0.4	0.4	0.5	0.5	0.8	0.8	1.1
Italy	0.0	0.0	0.1	0.1	0.2	0.3	0.3	0.3	0.3	0.3	0.4	0.5
Germany	0.9	1.8	1.8	1.5	1.8	1.7	2.8	4.2	5.2	5.2	5.3	5.3
France	0.0	0.0	0.1	0.2	0.4	0.4	0.5	0.8	0.7	1.3	2.4	3.6



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Japan	-	1	3	8	15	17	17	17	18	25	31	32
US	14	34	65	73	74	880	1,752	1,453	1,315	1,301	1,293	1,288
UK	0	11	21	29	32	34	36	42	55	51	51	51
Spain	1	8	18	24	31	32	36	39	39	38	40	43
Italy	2	3	6	11	17	18	21	23	24	21	22	23
Germany	36	89	111	111	150	180	178	179	188	184	184	185
France	5	8	16	35	58	60	74	67	66	84	106	120

SU standard units; * historical data; - product unlaunched

(Source: Datamonitor)



“Competition between a biologic drug and a FOB is much more likely to resemble Brand-to-Brand competition” (FTC Report, June 2009)

Contents

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2. Guidelines on FOBs/biosimilars
3. Next steps of FOBs/biosimilars
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Possibility of FOBs of antibodies



nature biotechnology volume 26 number 9 September 2008

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Toward biosimilar monoclonal antibodies

Christian K Schneider & Ulrich Kalinke

To what extent is the existing framework for biosimilars in Europe likely to be applicable to monoclonal antibodies?

May be possible but outstanding challenge !!
More challenges along with technology
advancements
Needs of in-depth scientific advices by the
authority



Reditux vs. MabThera (Rituxan)

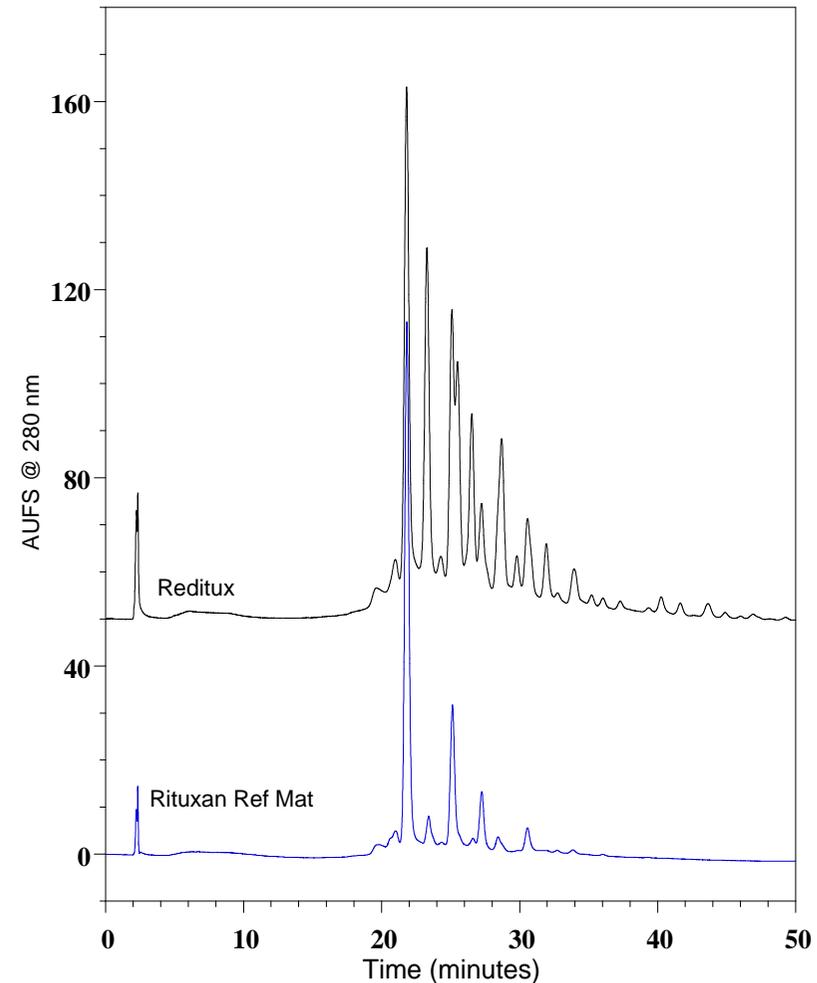


Reditux (Dr. Reddy)

Approved in India
April 30, 2007

- ◆ Same Amino Acid Sequence
- ◆ Host Cell Protein content much higher
- ◆ Content of aggregates not comparable
- ◆ Glycosylation not comparable
- ◆ Effector function not comparable
- ◆ Charge distribution not comparable
- ◆ Published clinical data with Reditux in NHL comprised only 17 patients

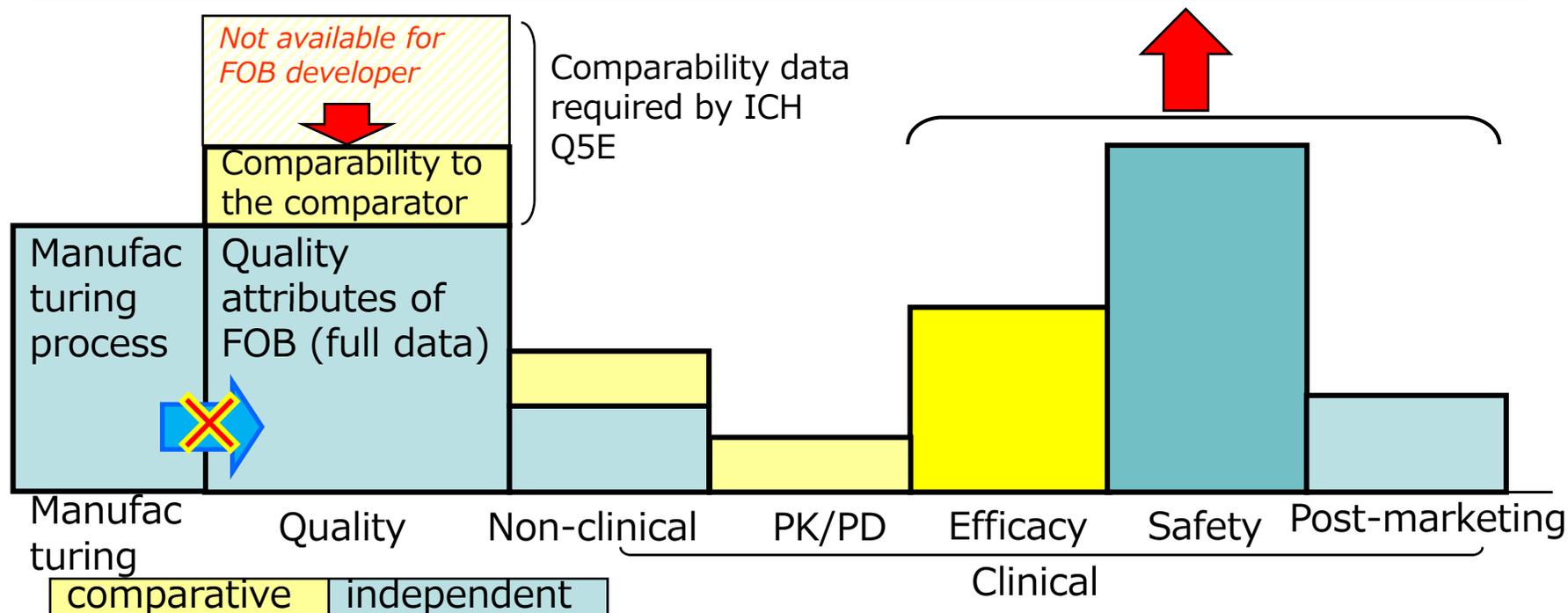
Different manufacturing -
Different drug -
Different safety/efficacy profile !?



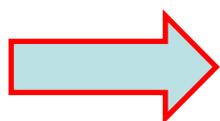
Comparison by Cation Exchange Chromatography

R. Harris (2008) presentation at „Biogenerics 2008“ Data source: Genentech (*Matt Field, Susan Gruerman*)

Development of Antibody FOBs

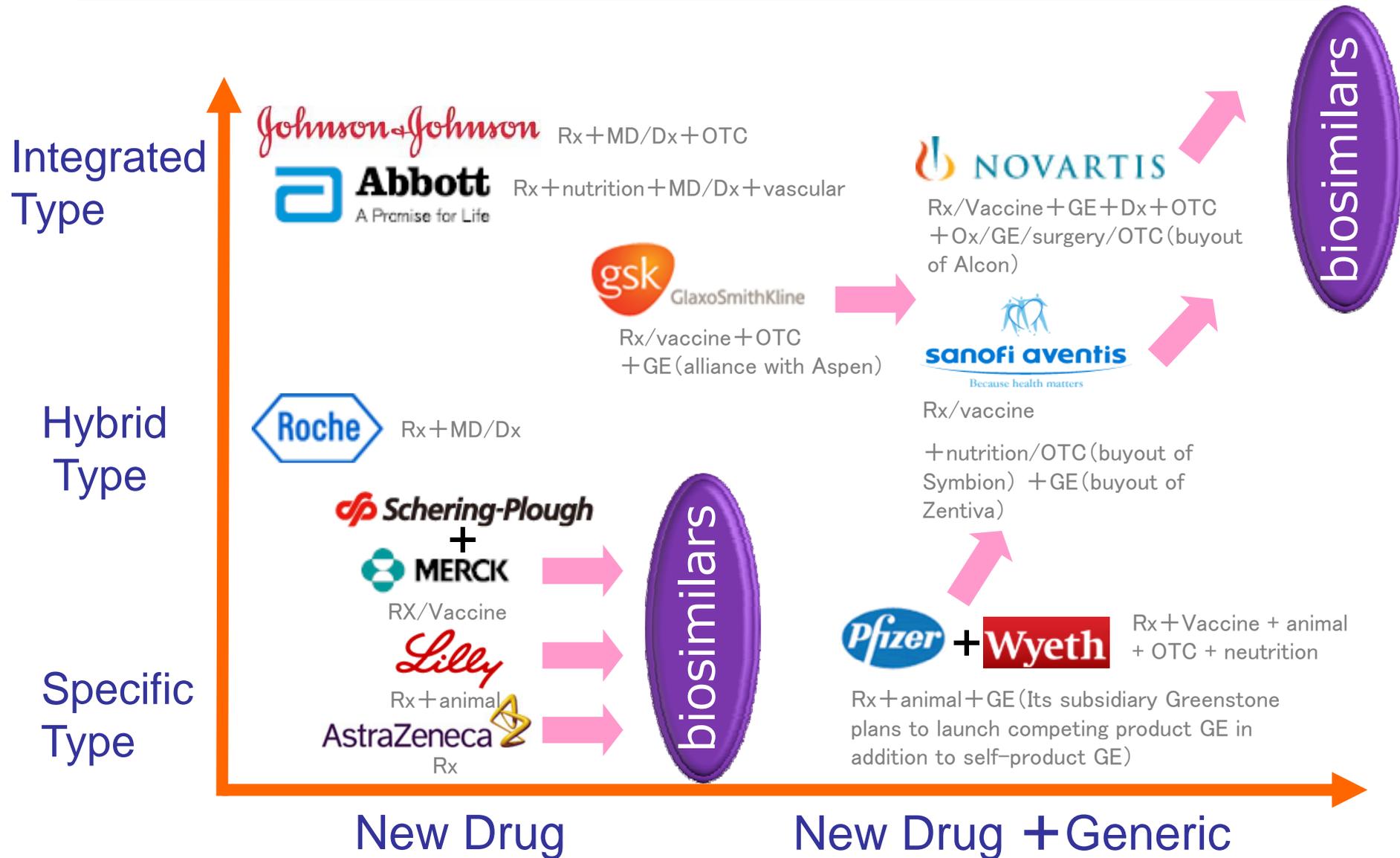


- ◆ May be possible to comparatively analyze of qualities by technology advancements of protein analysis
- ◆ Still difficult to prepare similar (comparable) products from different manufacturing process
- ◆ Needs to confirm efficacy/safety profile by clinical studies (Stand-alone approach)



- ◆ Next generation against the same antigen
- ◆ Cost reduction by high expression system

Global Major's Biosimilar Strategies



Today's Summary

- ◆ Brand and follow-on bioproducts are different substances
- ◆ Bioproduct is a mixture consisting of heterogeneous proteins and impurities and profile of the final product is much controlled by the manufacturing process.
- ◆ Traditional process for abbreviated approval of generic drugs cannot be applied. New guidelines for development of follow-on biologics entering after patent expiration are (being) established in many countries
- ◆ Patent expiration of bioproducts in the US, the biggest market of biologics, starts from 2013
- ◆ FOB guideline will be established after 2010, however, its contents are not predictable. (level of data requirement)
- ◆ According to existing guidelines (EU, Japan), FOBs of antibodies would be required considerable evaluations by clinical trials on efficacy and safety.
- ◆ Main arena of FOBs/biosimilars will be the antibody drug market. Players are likely to be limited to current brand manufacturers and companies with similar capabilities.

Patient's benefits (efficacy/safety) should be the top prioritized issue.

Contacts:

Investor Relations Group

Tel: +81 (0)3-3273-0554 Fax: +81 (0)3-3281-6607

e-mail: ir@chugai-pharm.co.jp

Mac Uchida, Kae Maeda, Tomoko Shimizu, Yusuke Tokita