Still celebrating 8th Year Anniversary

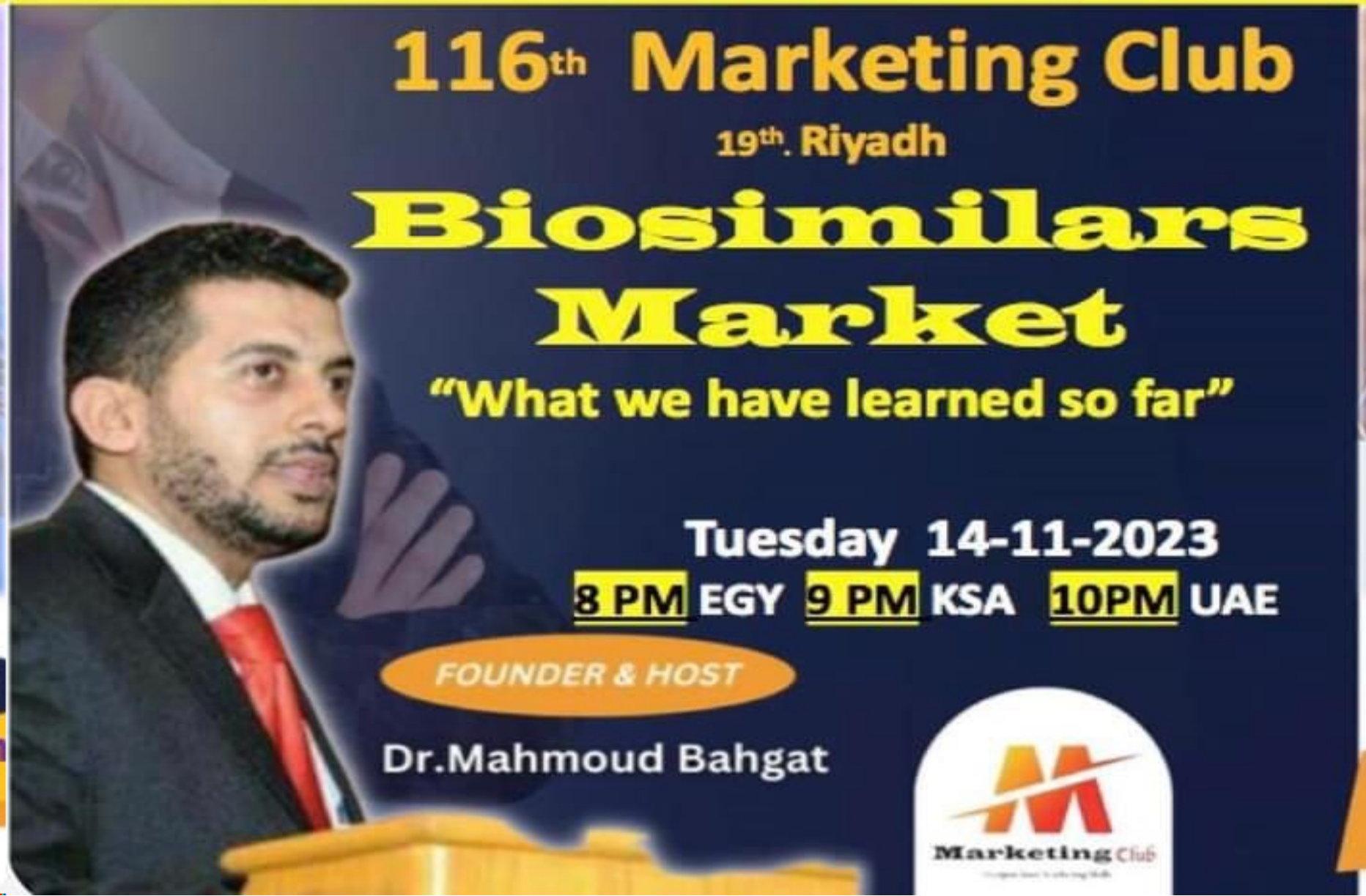
since 29-10-2015

116th Marketing Club

19th. Riyadh

Biosimilars Market

"What we have learned so far"



Tuesday 14-11-2023

8 PM EGY 9 PM KSA 10PM UAE

FOUNDER & HOST

Dr.Mahmoud Bahgat

Marketing Club

INSTRUCTOR

Dr.Mohamed Rohayem

Brand Manager

Biosimilars' Market What have we learned so far?

Mahmoud Rohaiem

Mohamed Rohayem

- MENA Brand Manager, Biotechnology Unite, Hikma Pharmaceutical.
- Pharmacist.
- Around 20 years of sales & marketing experience.
- Based in Riyadh, KSA.
- Married & have 3 kids.

Evolving Regulatory Landscape:

Regulations across markets evolving to favour biosimilars and reduce time and cost of development

FDA	EMA	MHRA
Regulatory framework 1st established in 2010 (BPCI)[1]	Regulatory framework 1st establish in 2003[5]	Waiver for non-clinical Pharmacology and Tox studies[8]
40+ biosimilars approved	90+ biosimilars approved*	Comparative efficacy study (Phase III) waiver basis scientific rationale[8]
Waiver for non-clinical Pharmacology and Tox studies[2]	Waiver for non-clinical Pharmacology and Tox studies[6]	
Approval of Interchangeable Insulins without Phase III study[3]	All biosimilars are interchangeable with reference product and equivalent biosimilar[7]	
Approval of Interchangeable biosimilars without switching data (e.g. Coherus' bRanibizumab)[4]		

*Total no. of Biosimilar applications approved by EMA, includes withdrawn/refused products. Sources: 1. GaBi(2023); 2. FDA Modernization Act 2.0(2023); 3. USFDA(2019); 4. Coherus(2022); 5. PubMed(2020); 6. EMA; 7. EMA/HMA(2023); 8. gov.uk

Evolving Regulatory Landscape in KSA* :

US FDA guidance

1996

Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products

APRIL 1996

EMA concept paper

1998

EMA biosimilar guidelines

2005

SFDA biosimilar legislation

2010

SFDA biosimilar guideline

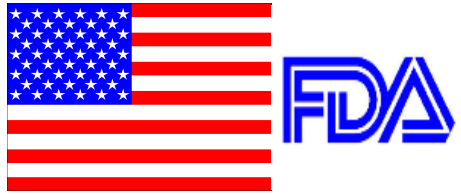
2017

Guideline on Biosimilar Products

Quality Considerations

*Evolution of Biosimilar Regulation in Saudi Arabia - Global Bio Conference Seoul - 1 September 2023

Biosimilarity: Regulatory Definitions



- **The American Food & Drug Administration (FDA)**: A biosimilar is a biological product that is highly similar to and has no clinically meaningful differences from an existing FDA-approved reference product.(1)

- **European Medicines Agency (EMA)**: A biosimilar medicine ('biosimilar') is a medicine highly similar to another biological medicine already marketed in the EU 'reference medicine'. Due to the natural variability of the biological source, strict controls are always in place during manufacturing to ensure that minor differences do not affect the way the medicine works or its safety. (2)

1. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm580419.htm#biosimilar
2. Biosimilars in the EU, Information guide for healthcare professionals

Why ‘biosimilar’ not ‘bioidentical’?

- Microheterogeneity
  - An effect of the inherent variability of the biological system used for manufacture[1]
  - Resulting product is a mixture of different forms of the same protein[2]

- Post-translational modifications[3]
  - Glycosylation, methylation, oxidation, deamination
  - May occur after a change in cell line or manufacturing process
  - Resulting product is highly similar, but not identical to the originator
  - Make complex molecules, such as mAbs and –cept fusion proteins, particularly difficult to replicate

But...originator products are also subject to variability[4]

1. Weise M, et al. Nat Biotechnol 2011;29:690-3. 2. European Commission. What you need to know about biosimilar medicinal products. A consensus information document. [Accessed September 2014]. http://ec.europa.eu/enterprise/sectors/healthcare/files/docs/biosimilars_report_en.pdf
3. Dörner T, et al. Ann Rheum Dis 2013;72:322-8. 4. Schneider CK. Ann Rheum Dis 2013;72:315-8.

Manufacturing Changes Authorized by EMA

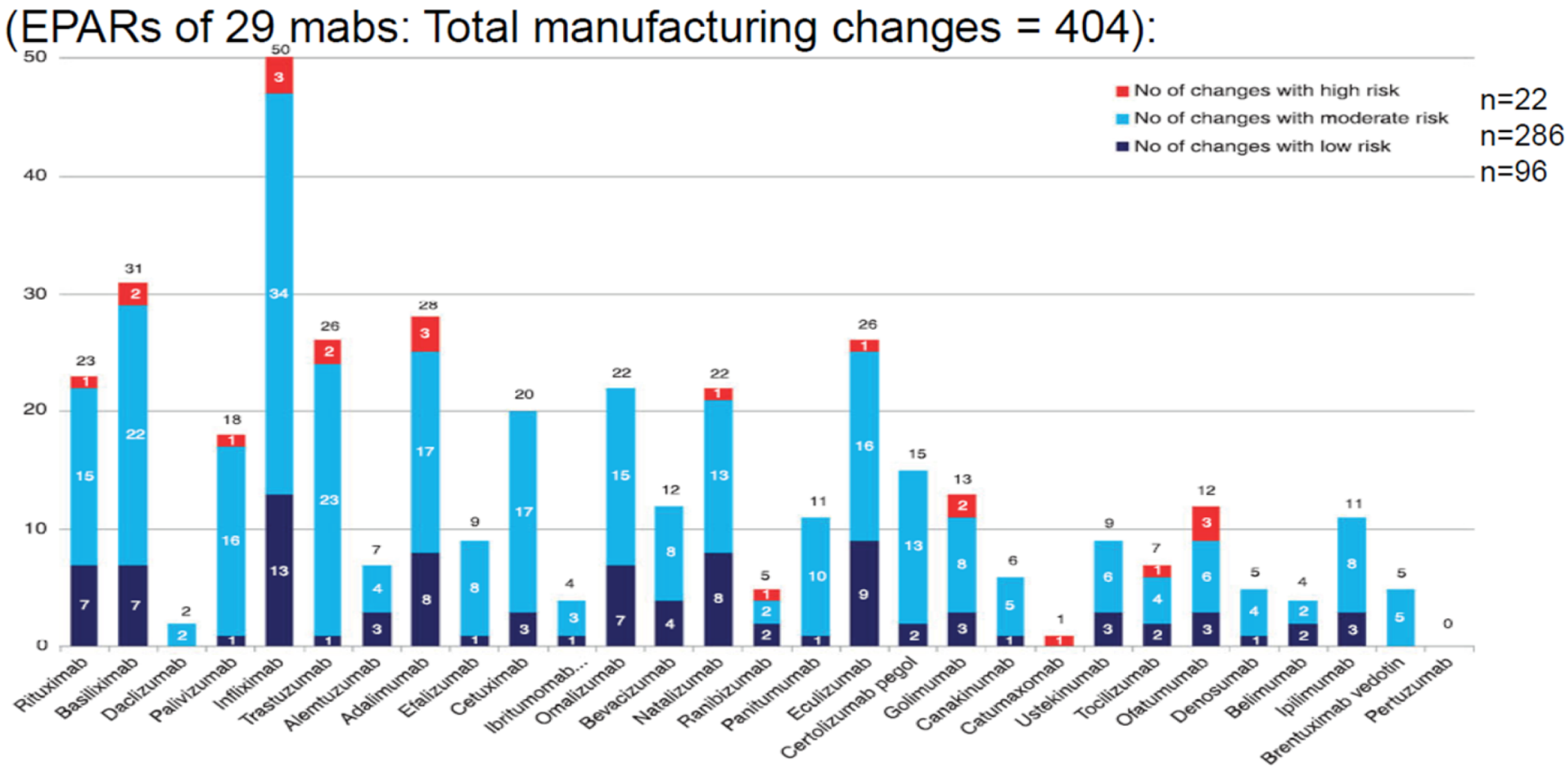
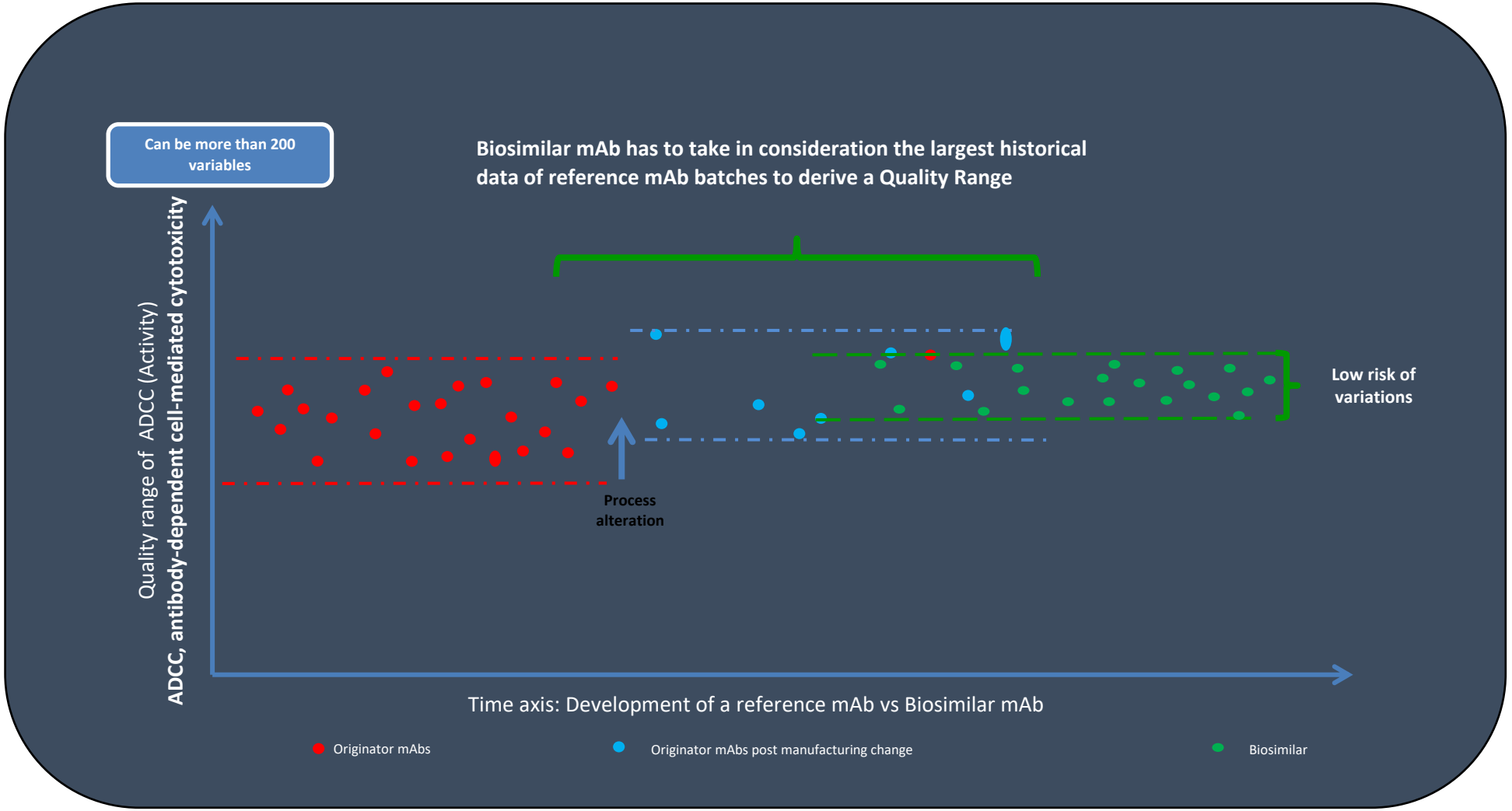


Figure 2. Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category (during the search period all non-proprietary names relate only to the trade named medicines listed in Table 1).

Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents.

1. Vezér B, Buzás Zs, Sebeszta M, Zrubka Z.: Curr Med Res Opin. 2016 May;32(5):829-34

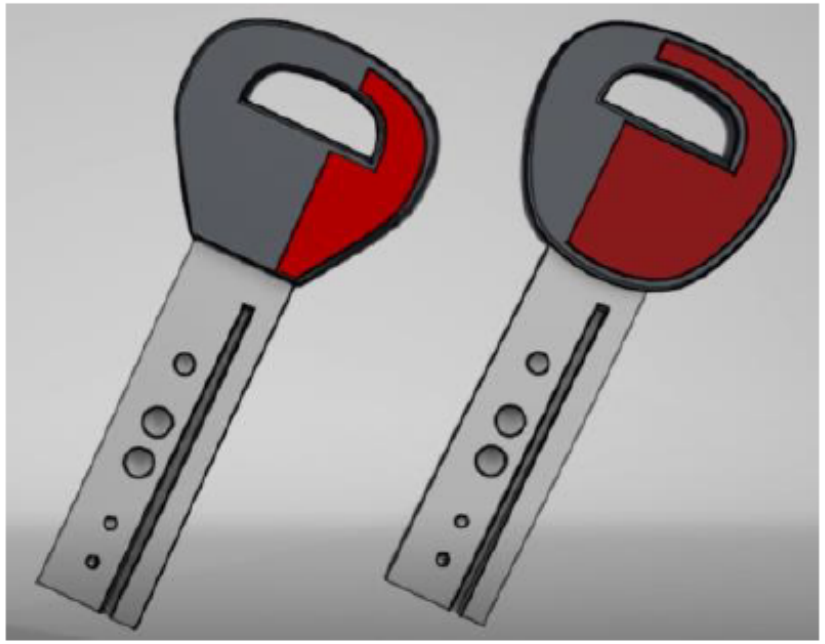
Manufacturing Changes Authorized by EMA



McCamish M, et al. Clin Pharmacol Ther. 2012;91(3):405-417. Figure adapted from: McCamish M, et al. MAbs. 2011;3(2):209-217.

Does it have to be 100% Identical?

Not identical



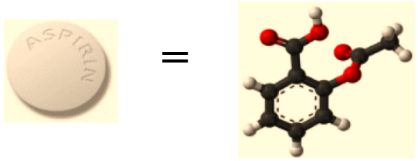
Structurally irrelevant difference

Both keys work

How Biologics Are Different In Comparison To Chemical Medicines?

In comparison to small chemical molecules, biologics are large, and they are often 200 – 1000 times larger than the chemical molecules. Moreover, biologics are significantly more complex with 3D protein structured.(1)

Aspirin
(Acetylsalicylic acid)
180 Daltons



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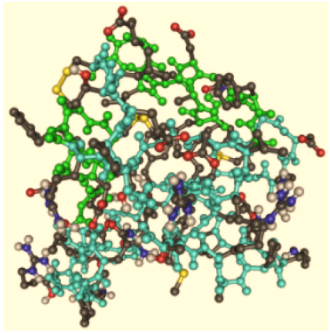
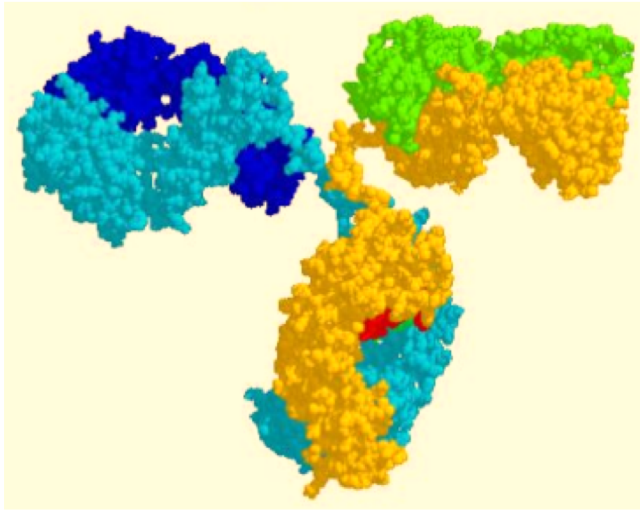
Insulin
5,700 Daltons



mAb
150,000 Daltons



1. 1.FDA. What are “Biologics” Questions and Answers. [Accessed September 2014]. http://www.fda.gov/AboutFDA/default.htm

Why ‘Biosimilars’ Are Not ‘Generic Drugs’?

Biosimilars differ from generics in complexity, manufacturing processes, and in the data needed to demonstrate similarity for approval1,2-3

Properties	Generics	Biosimilars
Size	Small	Large
Molecular Weight	~150 Daltons	~150,000 Daltons
Structure	Simple and well-defined	Complex with potential structural variations
Manufacturing	Predictable chemical process to make identical copy	Specialized biological process to make similar copy
Complexity	Easy to fully characterize	Difficult to characterize
Stability	Relatively stable	Sensitive to storage and handling conditions
Adverse Immune Reaction	Lower potential	Higher potential
Manufacturing Quality Tests	≤ 50	≥ 250
Approval Requirements	Small clinical trials in healthy volunteers	Large clinical trials in patients

1.Camacho LH, Frost CP, Abella E, Morrow PK, Whittaker S. Biosimilars 101: considerations for U.S. oncologists in clinical practice. Cancer Medicine. 2014;3:889-899. 2. Niederwieser D, Schmitz S. Biosimilar agents in oncology/haematology: from approval to practice. Eur J Haematol. 2011;86:277-288. 3. Alten R, Cronstein BN. Clinical trial development for biosimilars. Semin Arthritis Rheum. 2015;44:S2-S8.

Why ‘Biosimilars’ Are Not ‘Generic Drugs’?

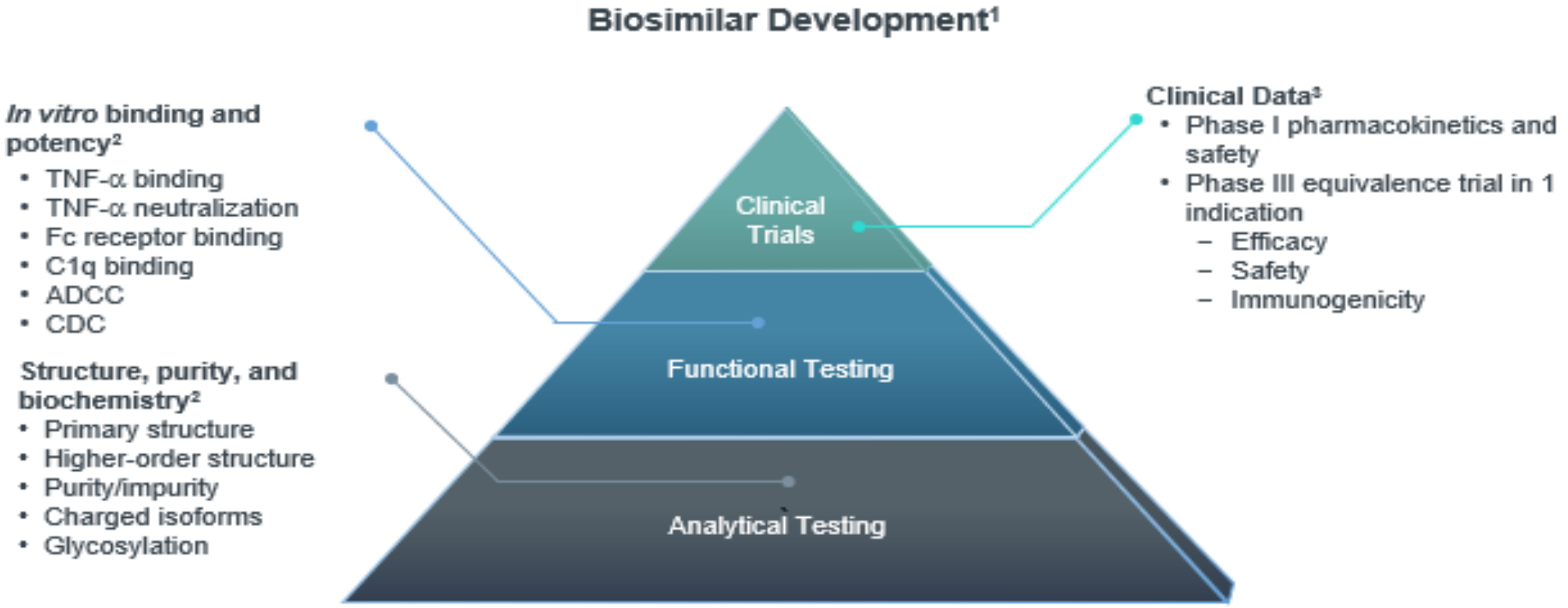
Biosimilars require significantly more expertise and investments to develop in comparison to small molecules

	Small Molecule Generics	Biosimilars
Expertise & Capabilities	- Easy to build given limited complexity	- Highly specialized skills - Experience with complex technological platforms
Development Spends	- Simple Gx: <$1 M - Complex Gx: $15-20 M	- $50M - $300M
Manufacturing Investments	- Simple Gx: $20-30 M - Complex Gx: $40-50 M	- $200 M+
Development Timelines	- 2 - 3 years	- 6 – 9 years
Clinical Studies	- Bioequivalence studies in healthy volunteers	- Pharmacokinetic comparison studies in Phase 3
No. of Subjects in Clinical Studies	- 20 – 50	- 100 - 500

Sources: McKinsey Aug’22 Report; BBL Research

Totality of the Evidence Concept:

Assessment of biosimilarity uses the “totality-of-the-evidence” concept, whereby a complete data package, comprising physicochemical, biological, nonclinical and clinical data, is used to evaluate and confirm biosimilarity between a proposed biosimilar and an approved originator (reference product).



ADCC, antibody-dependent cell-mediated cytotoxicity; C1q, complement factor 1q; CDC, complement-dependent cytotoxicity; Fc, fragment crystallizable;.

1. US FDA. Quality considerations in demonstrating biosimilarity of a therapeutic protein product to a reference protein product. 2015
2. EMA. Remsima Assessment Report. 2013.
3. US FDA. Scientific considerations in demonstrating biosimilarity to a reference product. 2015.

Development of a Biosimilar Requires a Paradigm Shift:

Reference medicine

Clinical

Functional testing

Analytical

Physicians' perception

The world turned upside down

Biosimilar

Clinical

Functional testing

Analytical

Scientific importance & regulatory requirements

At the end, both approaches provide the same level of confidence regarding safety and efficacy of the medicine

Extrapolation of Indications Concept:

Extrapolation of indications is a core principle of biosimilar development.
It is the leveraging of safety and efficacy data from clinical studies in the most sensitive indications to support the authorization of other less sensitive indications. Once extrapolation is granted, the biosimilar can be used for the treatment of all indications for which the reference product has been approved.[1,2]

EMA (2014)	FDA (2015)	WHO (2009)
• **Indication used in the clinical comparability should be the "most sensitive and relevant"**	• **Extrapolation should be based on sufficient scientific justification**	• If extrapolation is intended, a detailed **scientific discussion** on the benefit/risk should be provided
• Extrapolation of the results to the other indications would be possible, if the mechanism of action is the same.	• Efficacy and safety tested in **most sensitive indication** to detect clinically meaningful differences in safety and efficacy	• Efficacy and safety tested in **most sensitive indication**
• Extrapolation could be acceptable with **appropriate scientific justification** and considered in light of the **totality of data** from the biosimilar comparability testing		• Non-inferiority study design may not support extrapolation

Extrapolation is commonly possible with two following adequate justifications;

1. Mechanism of action does **not differ among different indications**.
2. Clinical studies should be conducted in **most sensitive and relevant indication**.

1. Bressler B and Dingermann T. Biosimilars 2015;5:41-48.
2. Curigliano G, O'Connor DP, Rosenberg JA, et al. Crit Rev Oncol Hematol 2016;104:131-137.

Studies Type Needed to Detect Biosimilarity:

- **Equivalence trial:**

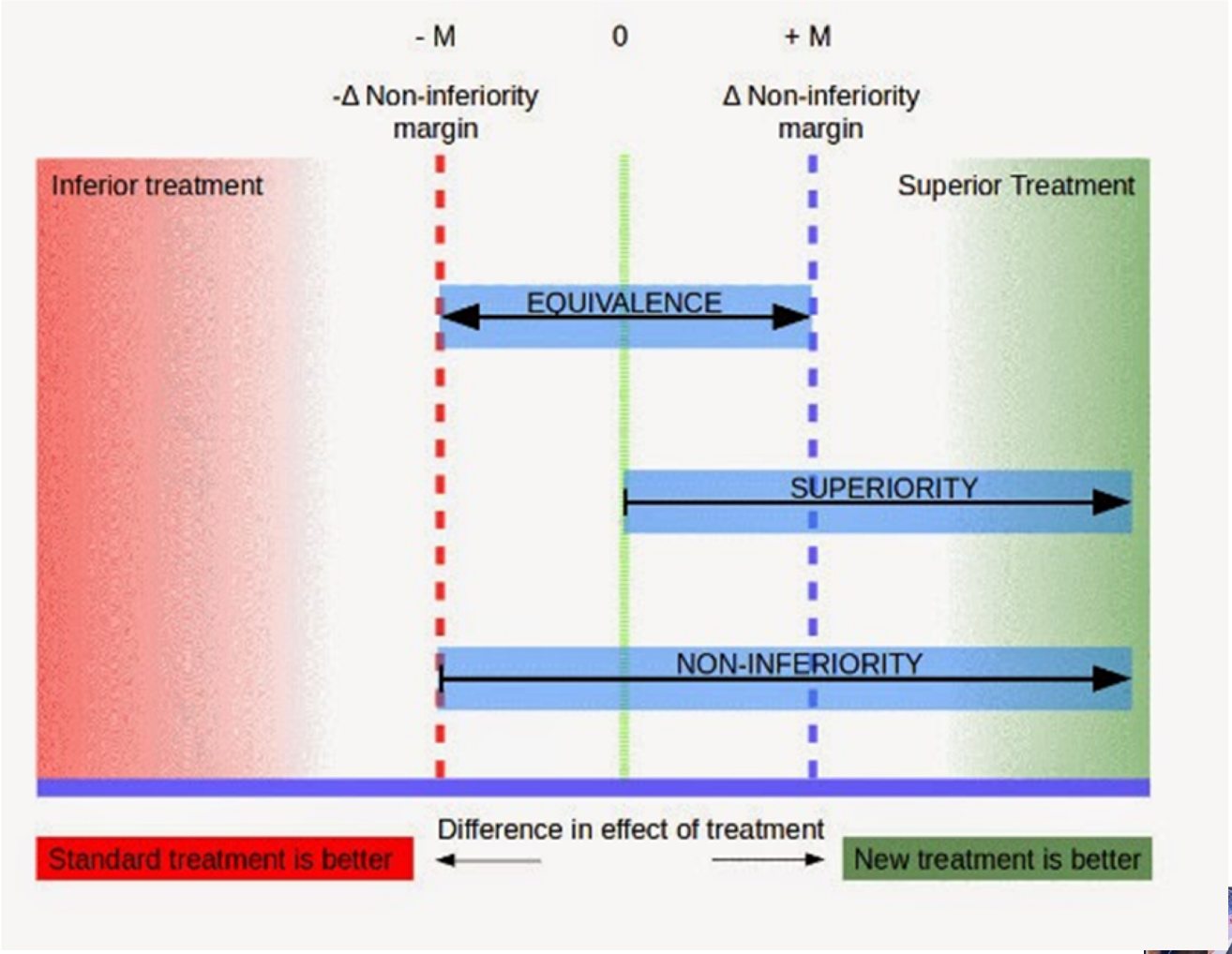
  To detect similarity based on predefined equivalence range.
  (predefined upper and lower bound)

- **Superiority trial:**

  To confirm superiority in terms of efficacy without compromising safety compared to the standard of care (SoC).
  (lower bound is equal to SoC, no upper bound)

- **Non-inferiority trial:**

  Are intended to show that the effect of a new treatment is not worse than that of an active control.
  (predefined lower bound, no upper bound)

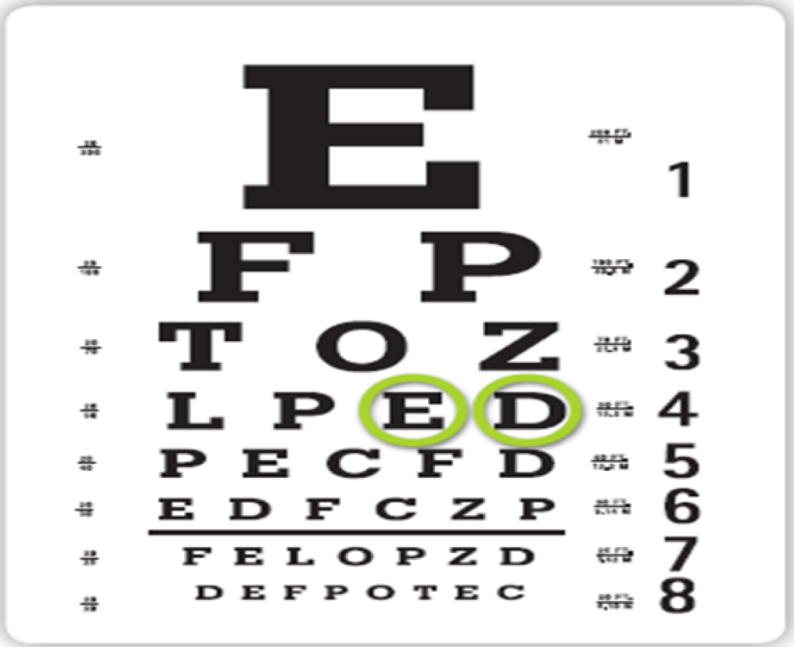


WHY Now !!!

STATE-OF-THE-ART ANALYTICS OF TODAY ENABLE PRECISE CHARACTERISATION OF ADVANCED BIOLOGICS

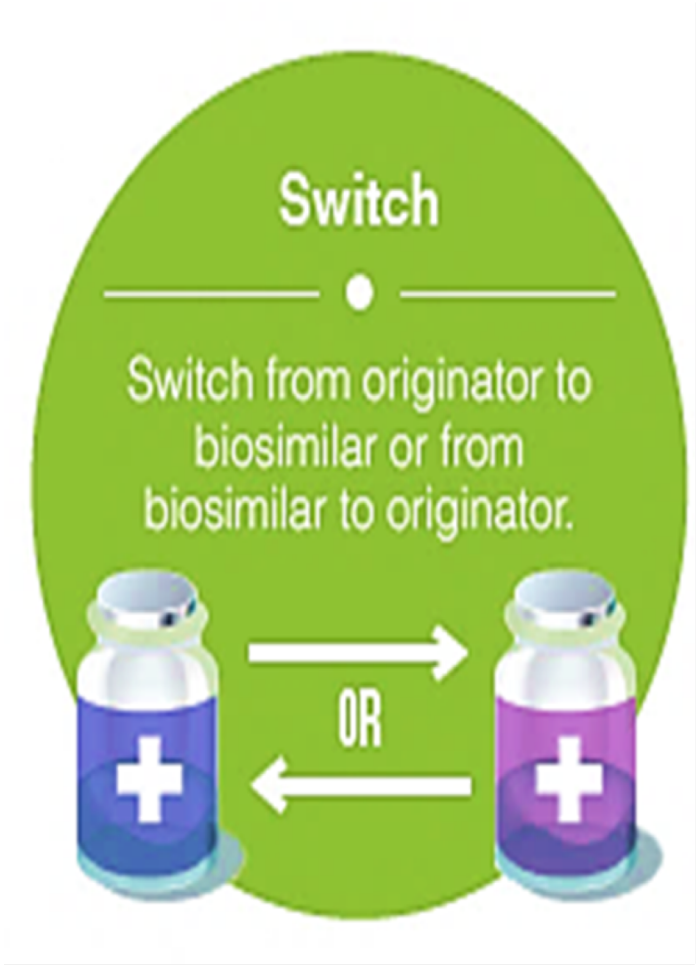
2000

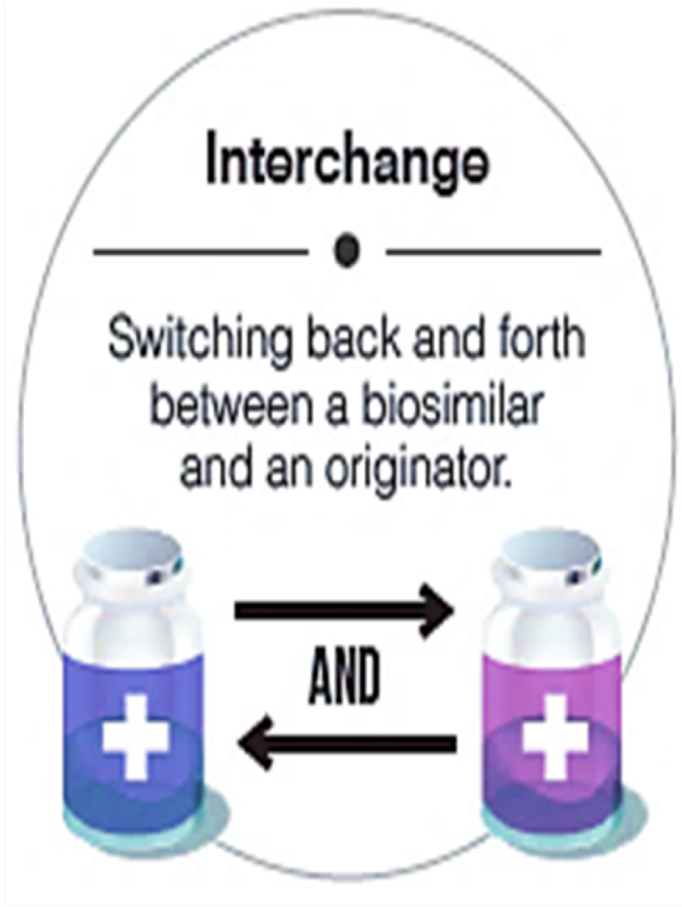
2015



WHEN RESOLUTION IS LOW, CRITICAL ATTRIBUTES CAN BE MISSED

Definitions of Switch, Interchange and Substitution:

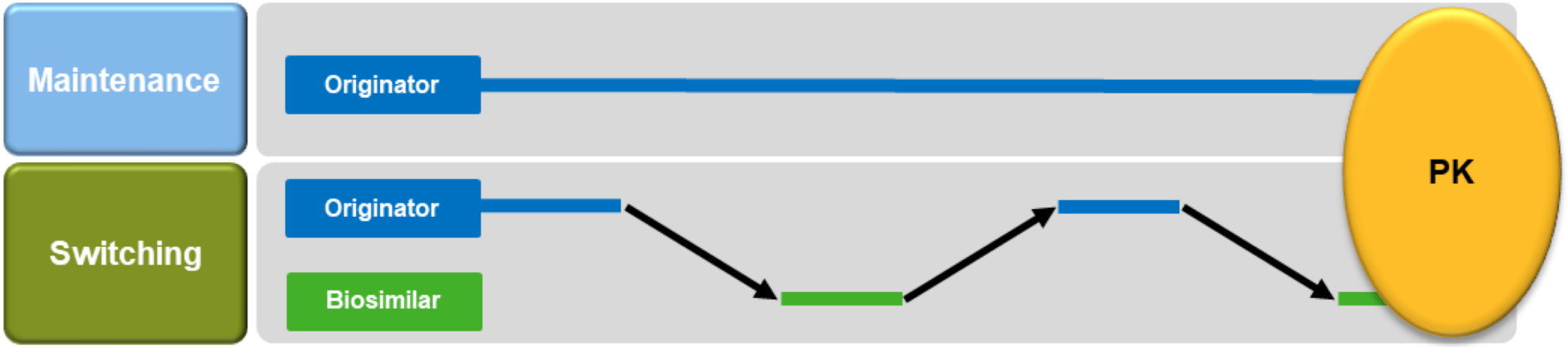




https://www.pharmashots.com/24011/top-biosimilar-companies-with-approved-and-pipeline-products-in-the-us-and-eu

Interchangeability (US FDA Guideline) :

- Switch study design



- Clinical Data Needed

Study Endpoints	Study Design	Study Population	Extrapolation	Route of Administration
- PK - PD - Immunogenicity - Safety	- Sample size based on PK - At least 2 doses both for reference and test drugs	Adequately sensitive population	Support extrapolation of data to other conditions of use	Assessment of clinical changes in safety risk & efficacy

FDA. Guidance for Industry. 2017

Interchangeability (EMA):

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

HMA
Heads of Medicines Agencies

19 September 2022
EMA/627319/2022

Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU

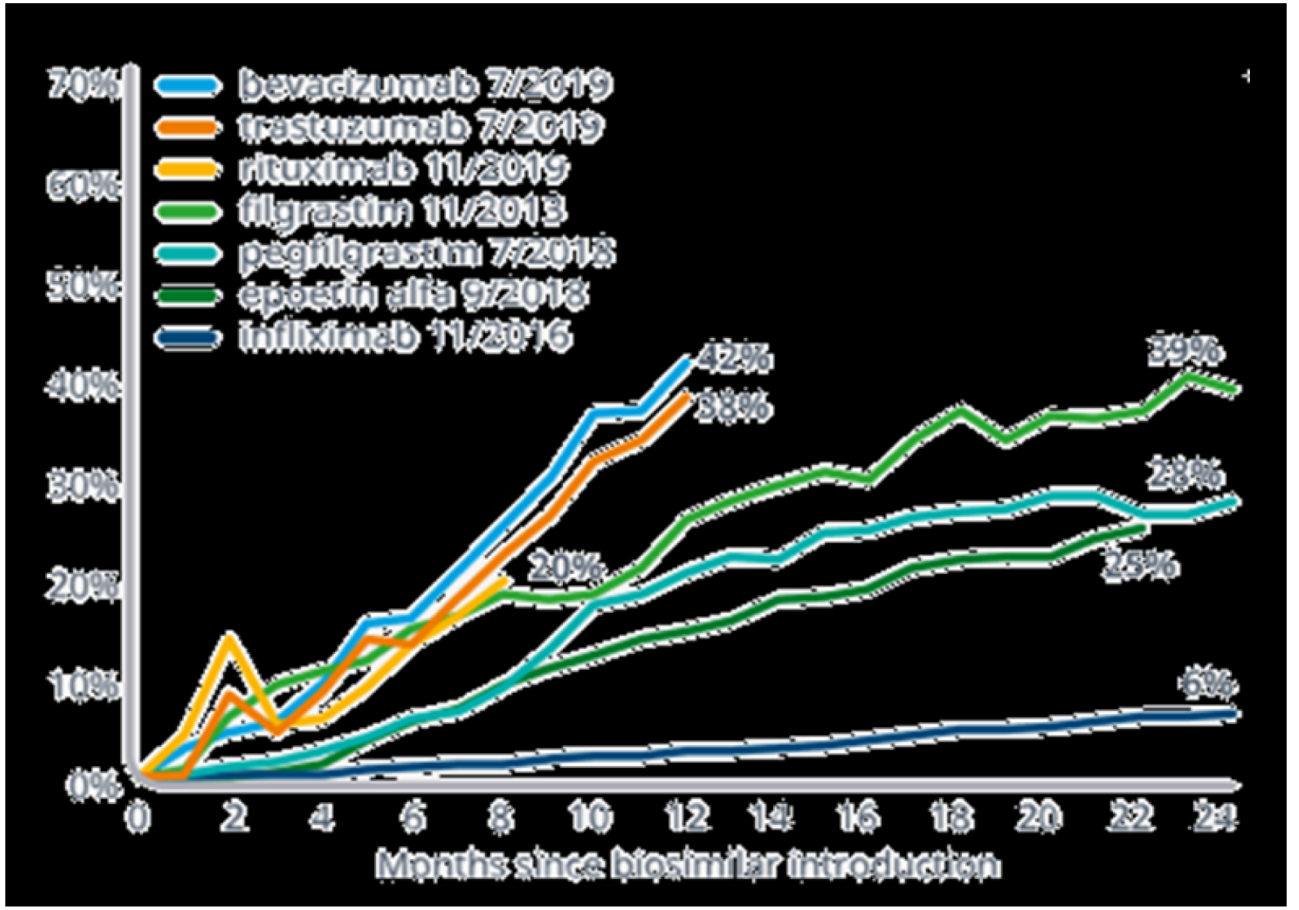
HMA and EMA consider that once a biosimilar is approved in the EU it is interchangeable, which means the biosimilar can be used instead of its reference product (or vice versa) or one biosimilar can be replaced with another biosimilar of the same reference product.

1Statement on the scientific rationale supporting interchangeability of biosimilar medicines in the EU
EMA/627319/2022

Biosimilars Main Players :

https://www.pharmashots.com/24011/top-biosimilar-companies-with-approved-and-pipeline-products-in-the-us-and-eu

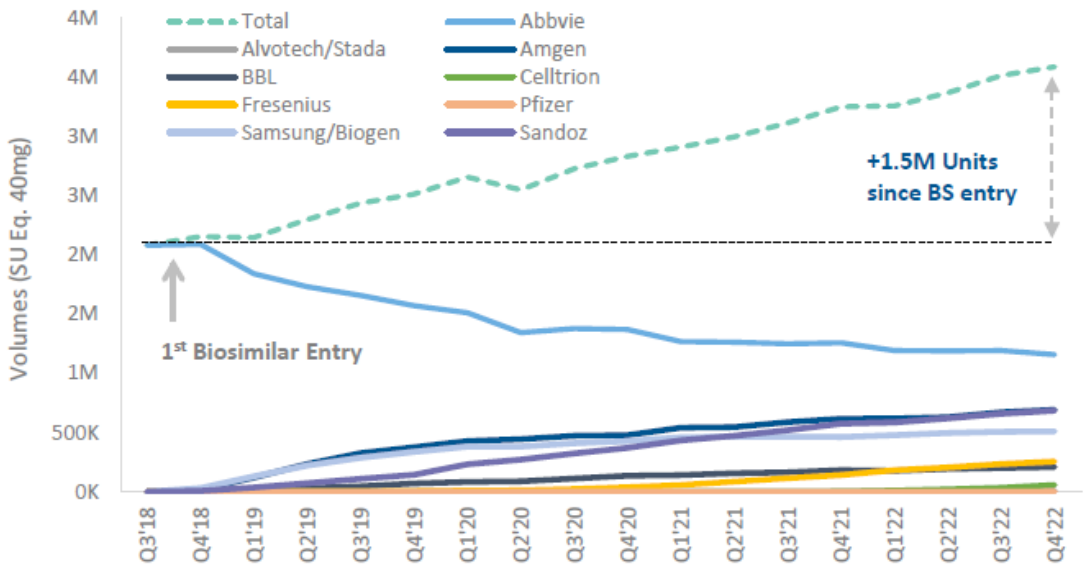
Recently Launched Biosimilars Have Significantly Higher & Faster Market Share than Prior Biosimilars[1]



[1]Biosimilars in the United States 2020–2024 Competition, Savings, and Sustainability. IQVIA, Sept 2020 (https://www.iqvia.com/insights/the-iqvia-institute/reports/biosimilars-in-the-united-states-2020-2024),

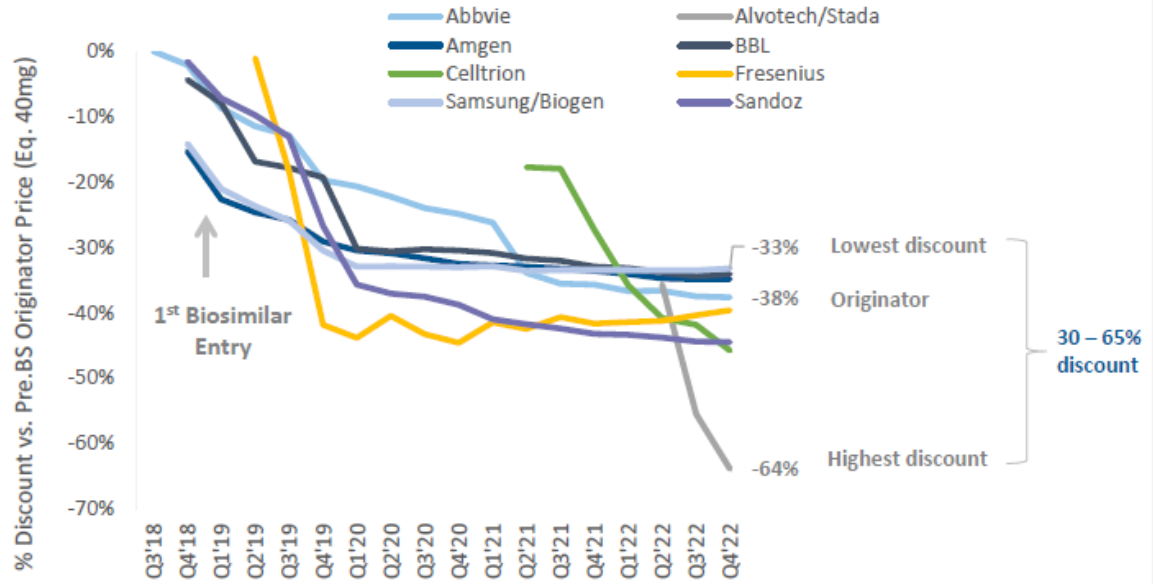
Biosimilars –Enabling Affordable Access to Biologics in Europe:

Example: Increase in EU Adalimumab Market Size (SU)



Market expanded at a 14% CAGR since launch of biosimilars in 2018

Example: Reduction in EU Adalimumab Pricing



Pricing has reduced by >60% in since the launch of biosimilars in 2018

Sources: IQVIA

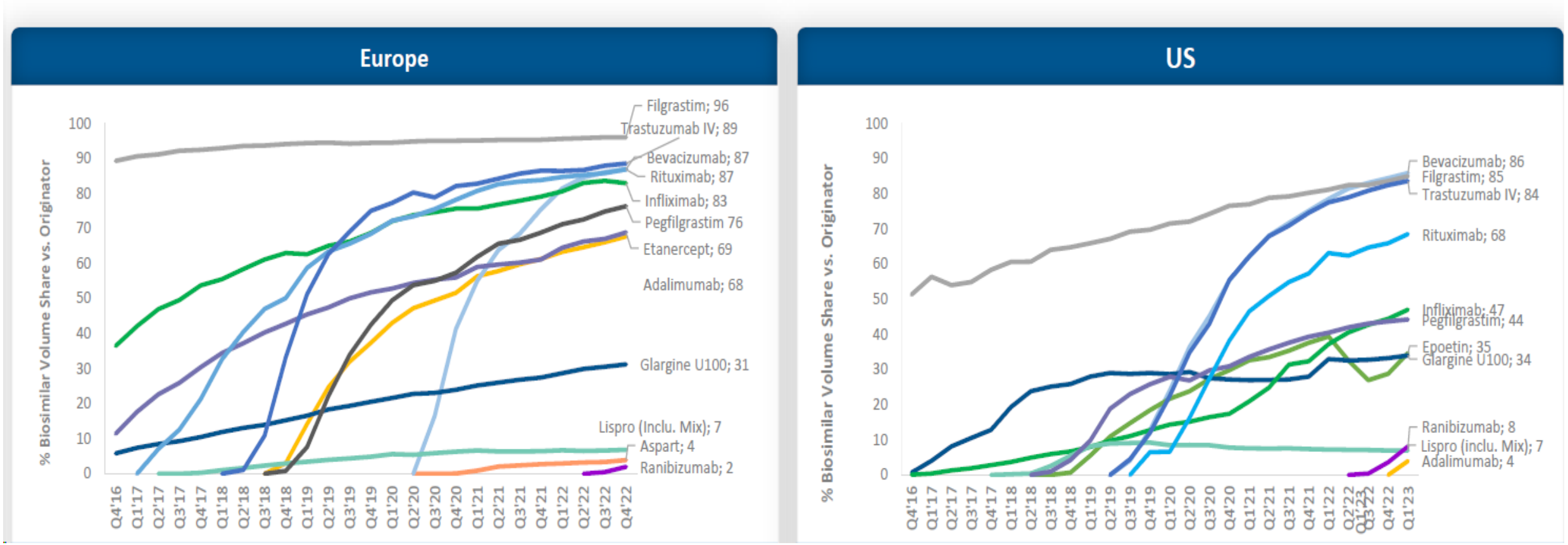
Biosimilars –Enabling Affordable Access to Biologics in KSA:

Units				
	2018	**2020**	**2023**	**CAGR%**
Infliximab	37,700	85,471	220,124	80%
Adalimumab 40mg	141,179	215,000	570,080	59%

Prices SAR				
	2018	**2020**	**2023**	**CAGR%**
Infliximab	765 / 725	698.75/562.5/515	…….	…….
Adalimumab 40mg	1,875	750/637.5/427	…….	…….

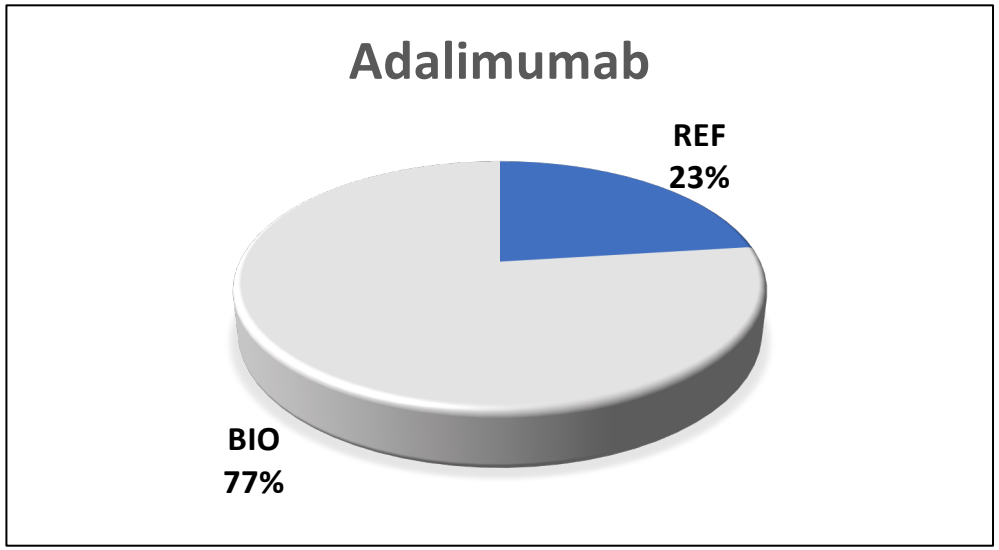
Sources: NUPCO Tender

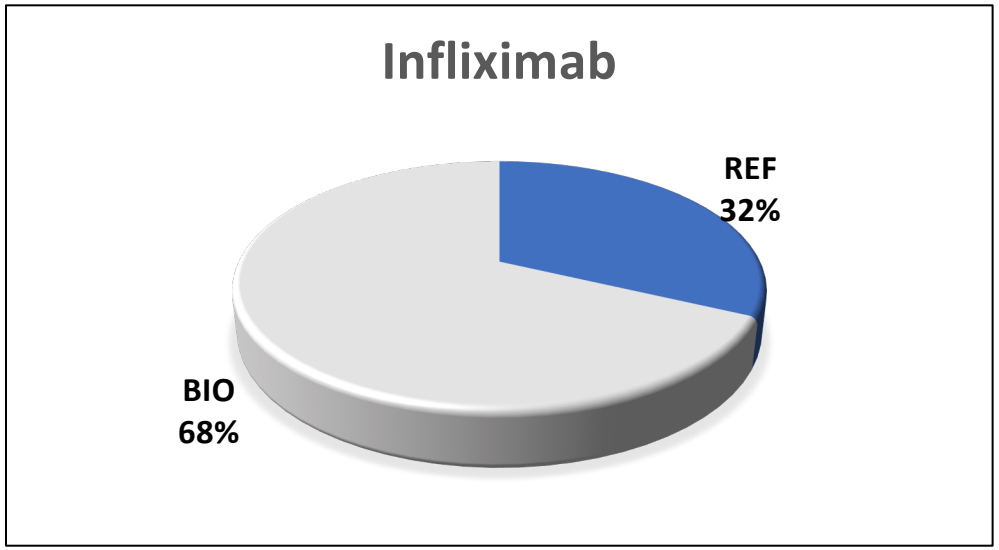
Biosimilar Adoption in Europe (Q4/22) vs US (Q1/23):

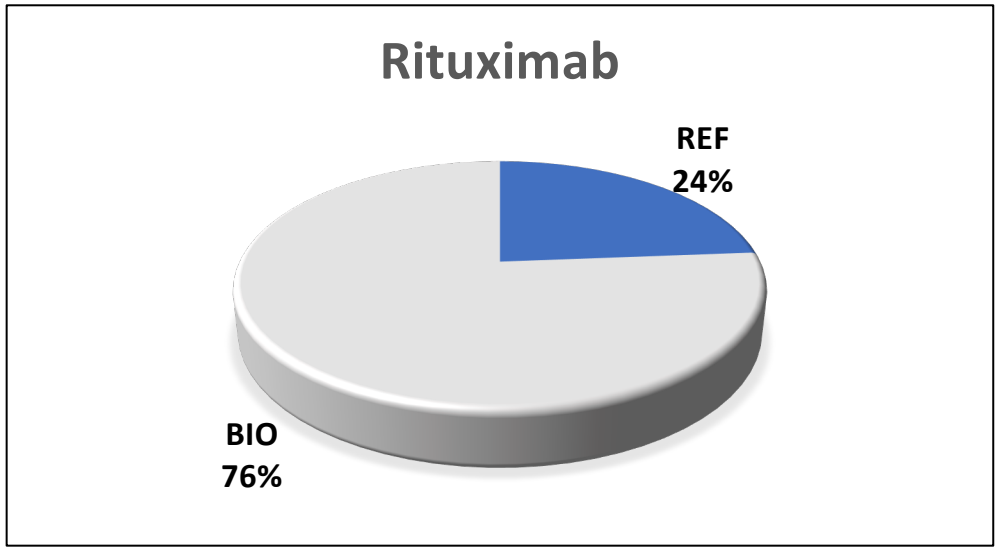


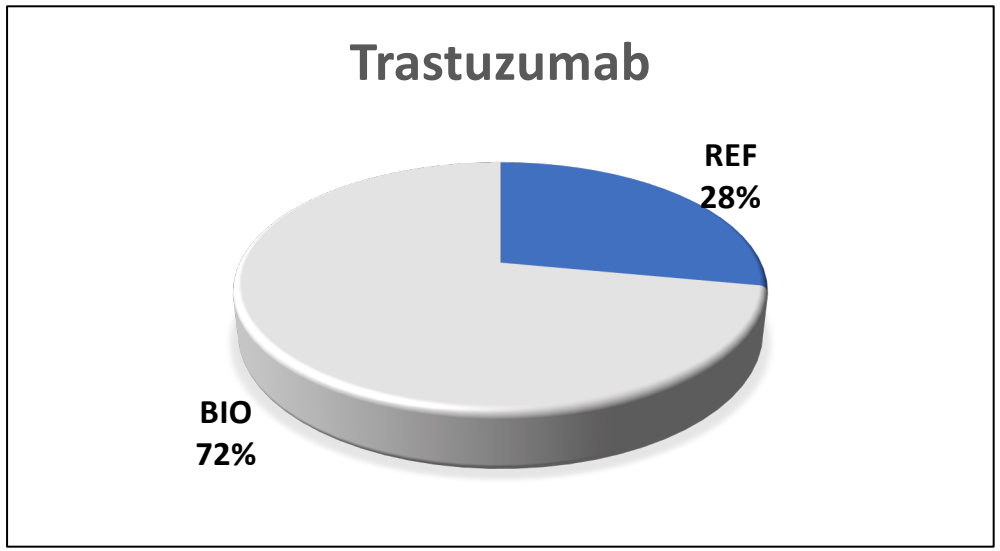
Source: IQVIA volumes (Eq.SU) (US: Till Q1’23; Europe: Till Q4’22)

Biosimilar Adoption in KSA YTD 09/2023:









Source: IQVIA SCIM YTD 09/2023

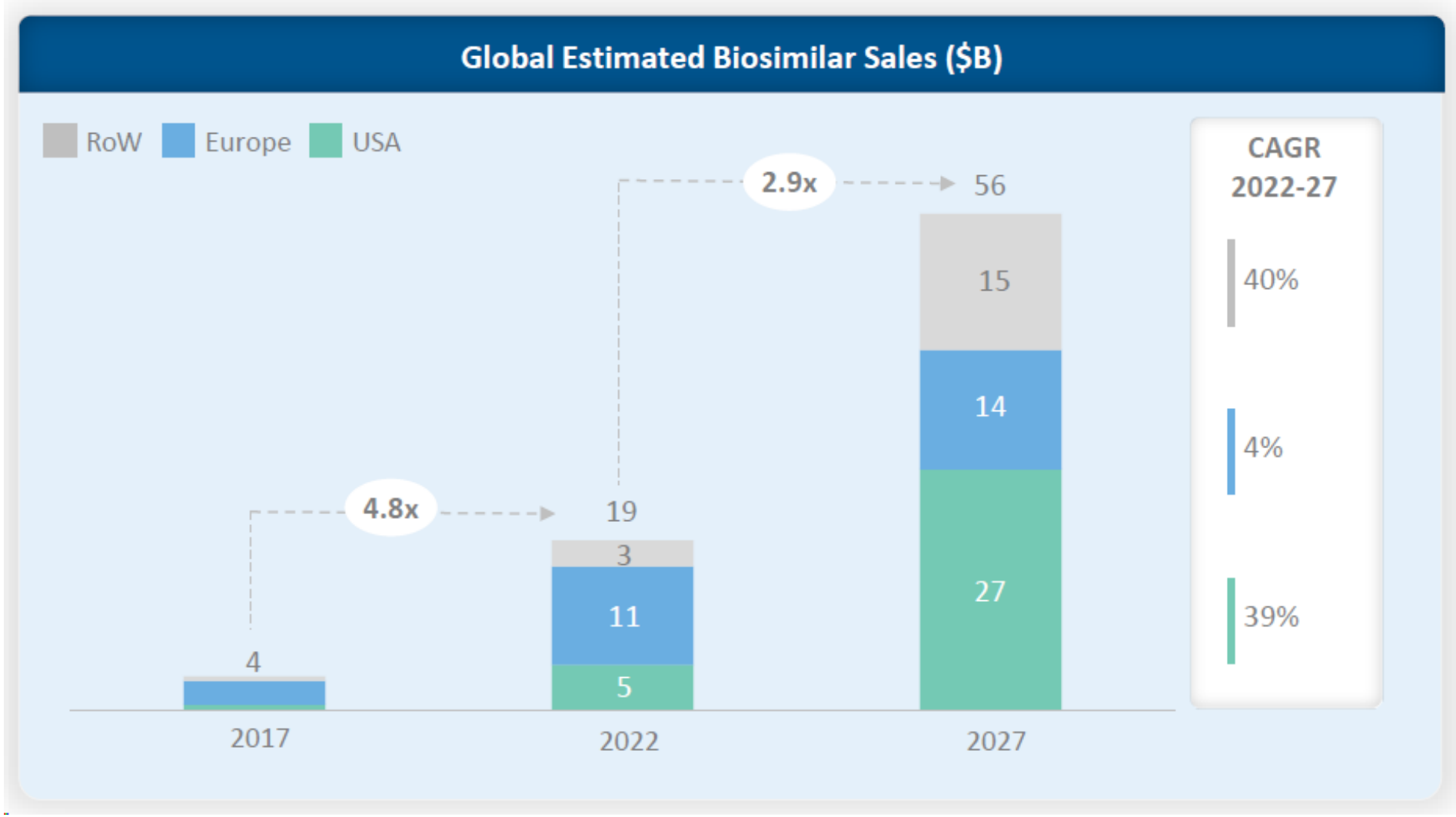
Biosimilars approved in Saudi Arabia

Class	Active biological substance	Number of biosimilars
Polysaccharides	Enoxaparin sodium	4
Growth factors	Epoetin	1
	Filgrastim	3
	Pegfilgrastim	4
Hormones	Follitropin alfa	1
	Insulin glargine	3
	Insulin aspart	1
	Somatropin	1
	Teriparatide	2
Monoclonal antibody	Adalimumab	6
	Infliximab	2
	Rituximab	2
	Bevacizumab	2
	Trastuzumab	6

*Evolution of Biosimilar Regulation in Saudi Arabia - Global Bio Conference Seoul - 1 September 2023

Global Biosimilar Market Size

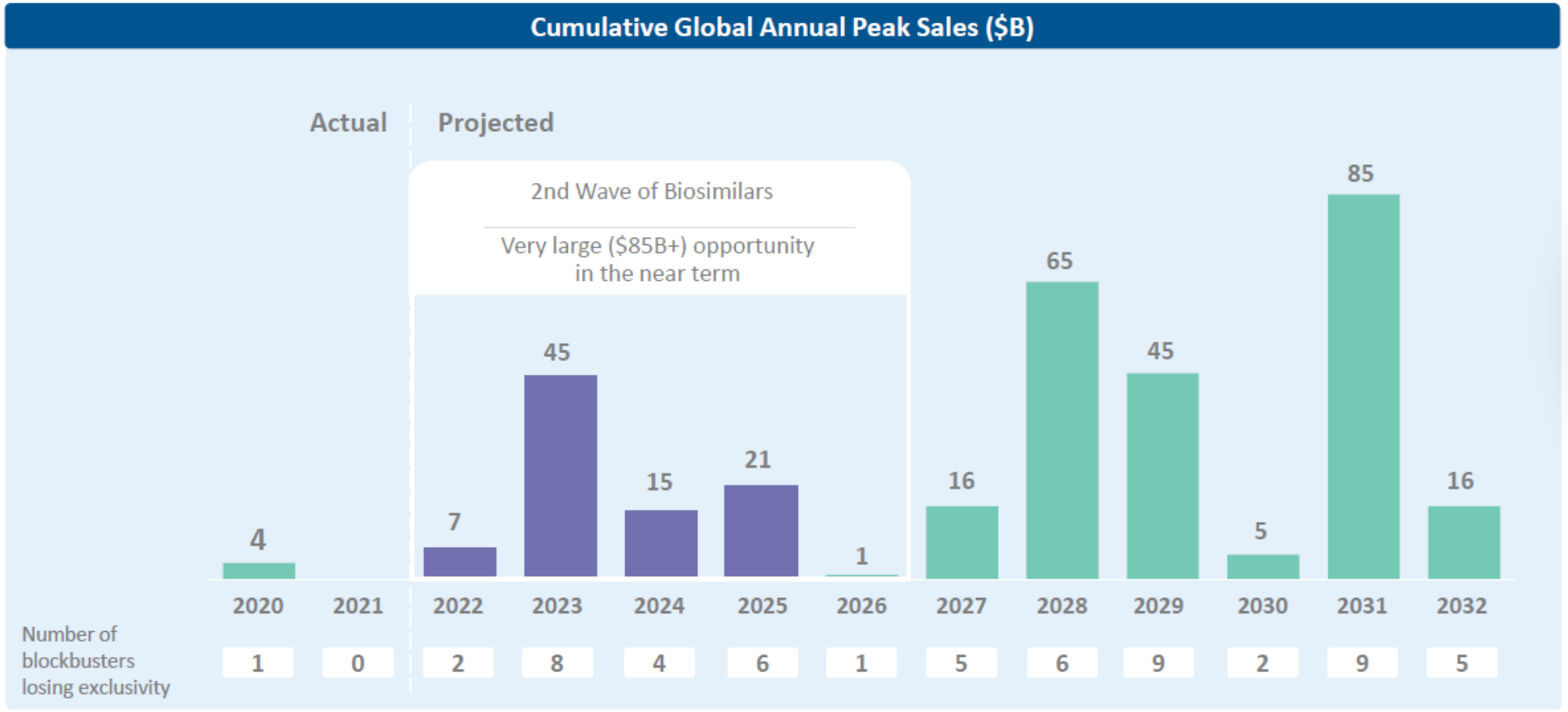
Market has grown 5x vs. 2017 in last 5 years



Source: McKinsey BiosimCast2022

Global Biosimilars Opportunity Potential:

Very large opportunity with 55+ blockbusters losing exclusivity by 2032 translating to $270B+ in cumulative peak sales



2nd wave of biosimilars from 2022 – 2026 represent a $85B+ opportunity in the near term

Notes: *"Blockbuster" defined here as a drug with annual sales of more than $1 B in the peak year. Analysis based on timing of US patent expiry I Sources: EvaluatePharma, Jan 2023; Public disclosures; McKinsey analysis

Summary:

Biosimilars market expected to grow significantly to $56B by 2027

- Biologics becoming 'Standard of Care'
- Increased adoption of biosimilars
- 55+ products losing exclusivity within the next 10 years

Launch of biosimilars improves access and affordability

- Market expansion as they become more affordable for a larger patient population
- Lower costs translate to significant savings

Regulatory landscape likely to evolve to further increase uptake of biosimilars

- Removal of Phase III by several other regulators
- Automatic substitution

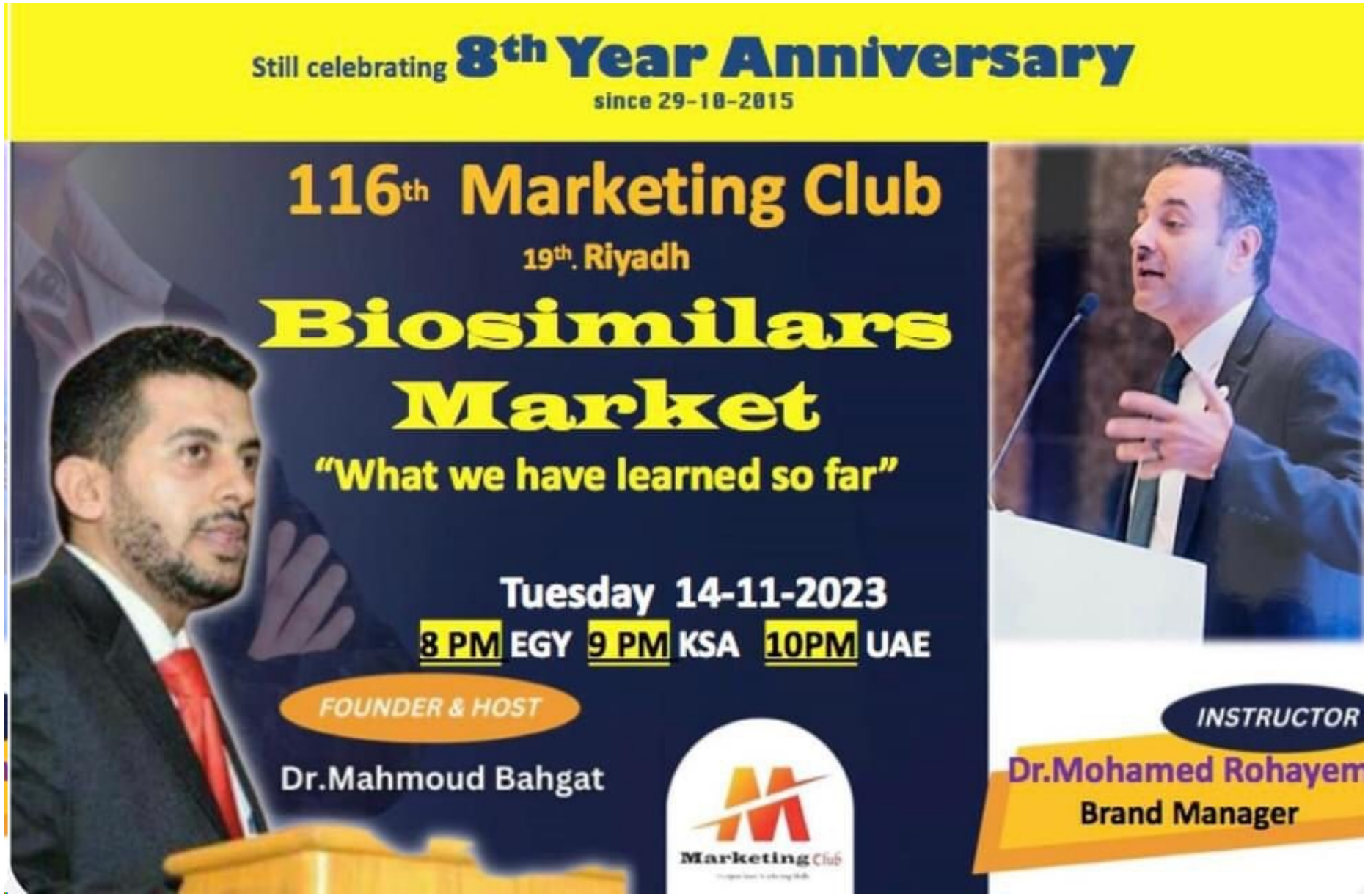
As competition increases, cost competitiveness will be key to success

- Vertical integration and scale will be key levers of cost leadership

Important Links :

- https://www.gabionline.net/
- https://www.centerforbiosimilars.com/
- https://pharmaintelligence.informa.com/searchlisting?searchtext=biosimilars

Thank You


Still celebrating 8th Year Anniversary
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Biosimilars Market
"What we have learned so far"
Tuesday 14-11-2023
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FOUNDER & HOST
Dr.Mahmoud Bahgat
Marketing Club
INSTRUCTOR
Dr.Mohamed Rohayem
Brand Manager