ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI MEDICINA SPECIALISTICA, DIAGNOSTICA E SPERIMENTALE

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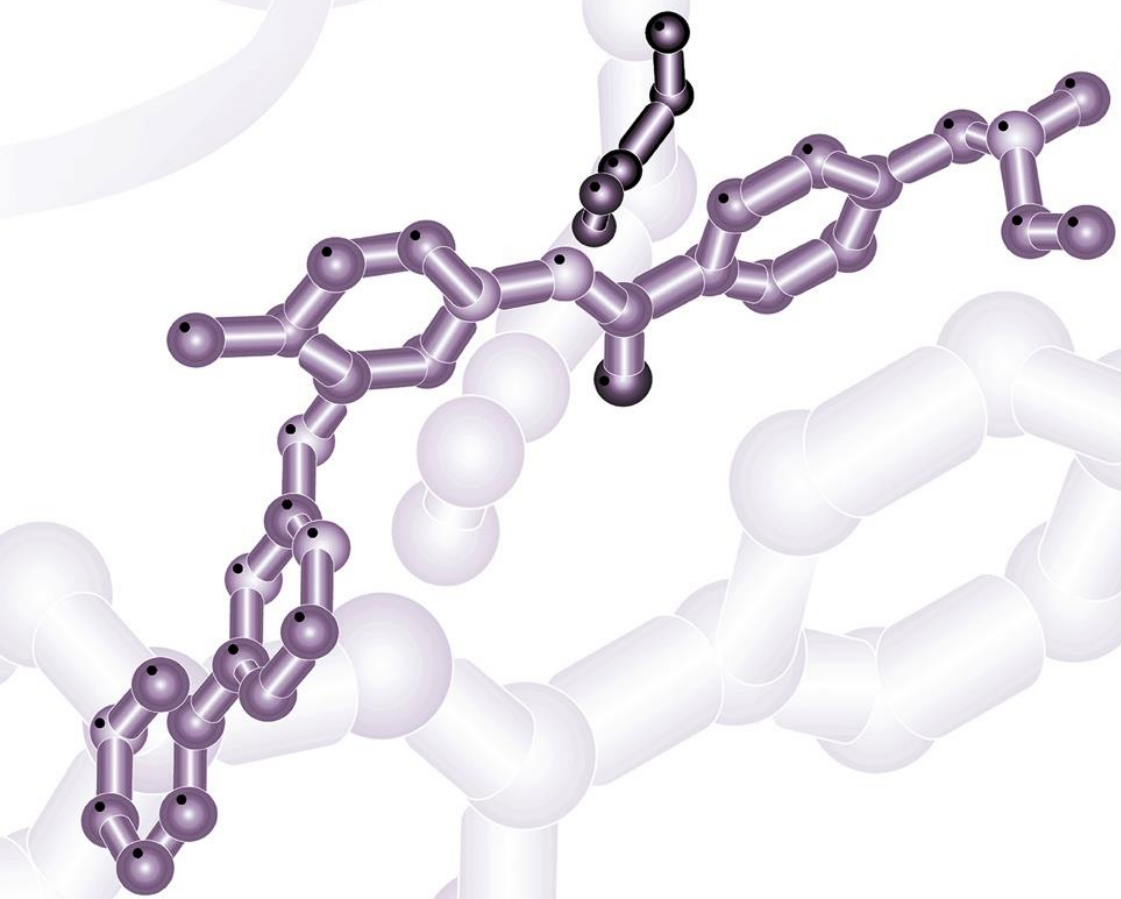

New Drugs in Hematology

President: Pier Luigi Zinzani

Co-President: Michele Cavo

Bologna,
Royal Hotel Carlton
May 18-20, 2022

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

DISCLOSURES: PROF. WOJCIECH JURCZAK, M.D., PH.D.

ADVISORY BOARDS : Astra Zeneca, Beigene, Janssen, Sandoz

RESEARCH FUNDING: Astra Zeneca, Bayer, Beigene, Celltrion, Hutchmed, Janssen, Sandoz, TG Therapeutics,

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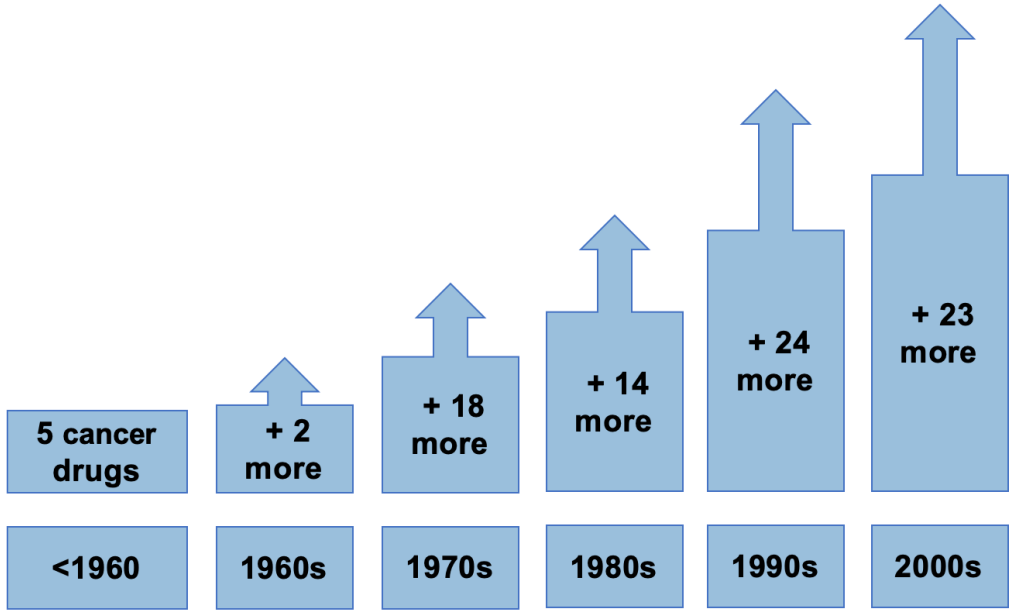
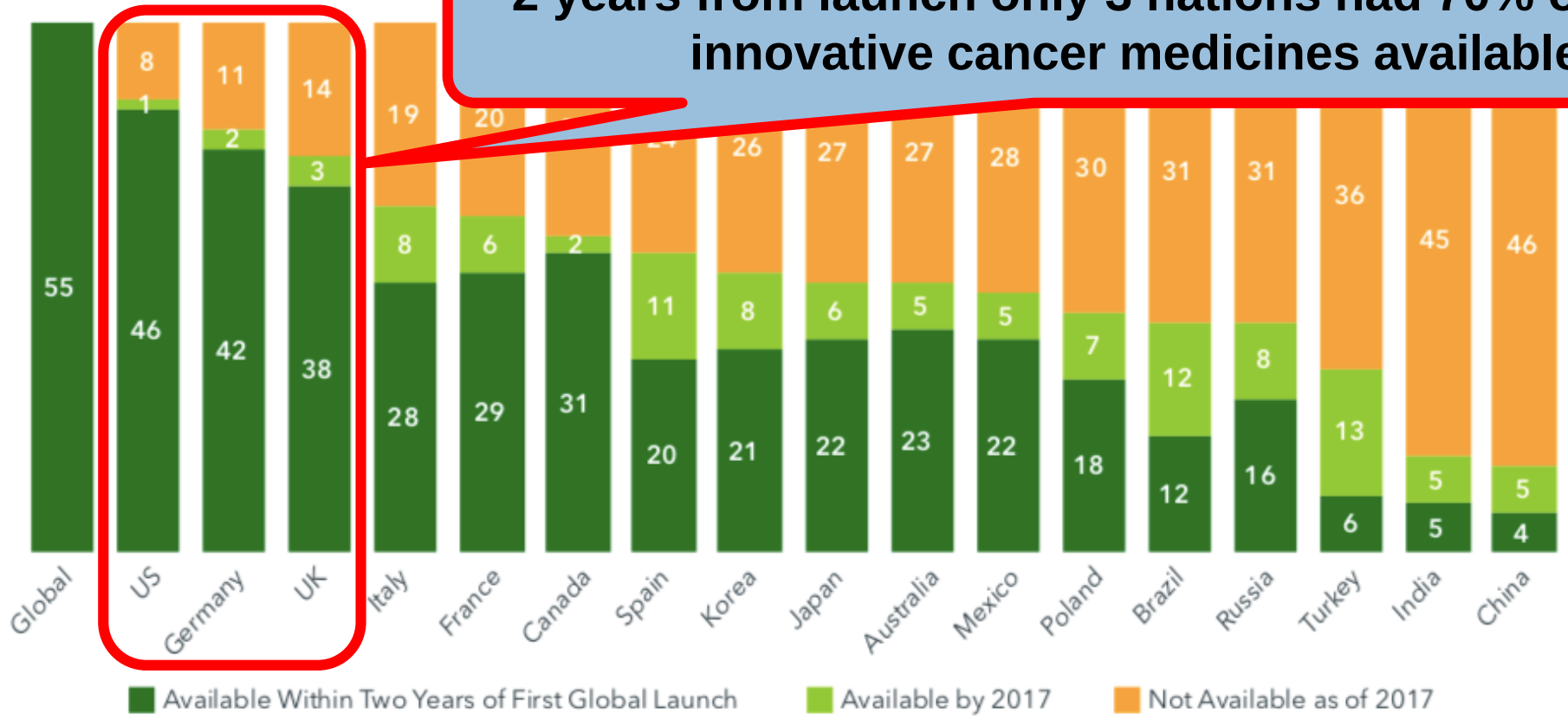
Rituximab Biosimilars

The number of available anti-neoplastic agents increases



The access to modern medical technologies is delayed

2 years from launch only 3 nations had 70% or more of innovative cancer medicines available [1]



Ref: [1]. Stott K. Pharma's broken business model: An industry on the brink of terminal decline. Endpoints news, November 28, 2017. https://endpts.com/pharmas-broken-business-model-an-industry-on-the-brink-of-terminal-decline/. Accessed March 7, 2019

Effective drugs ….

……. are those we may afford

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More affordable medicines: generics and biosimilars

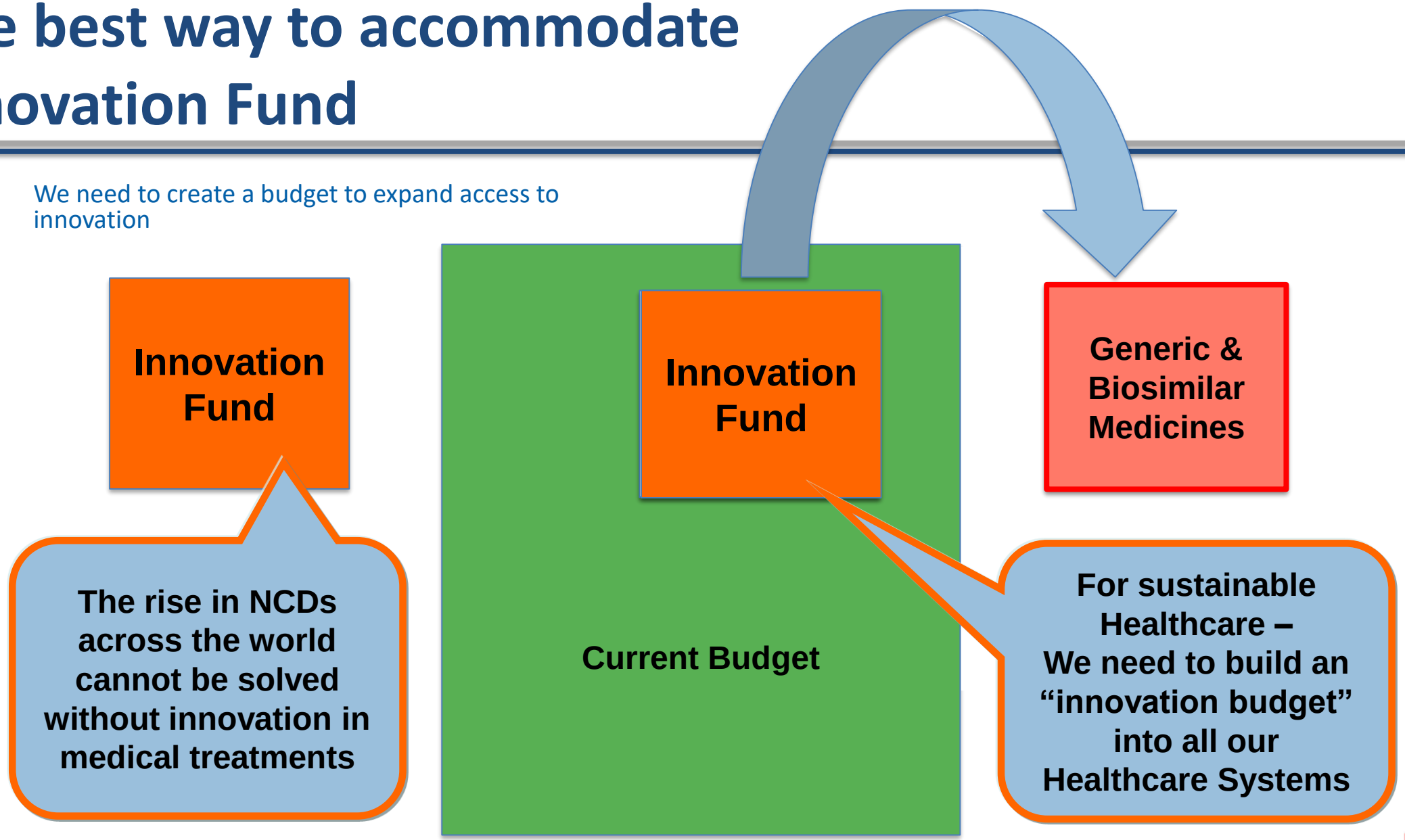
Small molecule → **Generic**
i.e. Acetylsalicylic acid - 21 atoms

Biological drug → **Biosimilar**
i.e. IgG1 antibody > 20,000 atoms

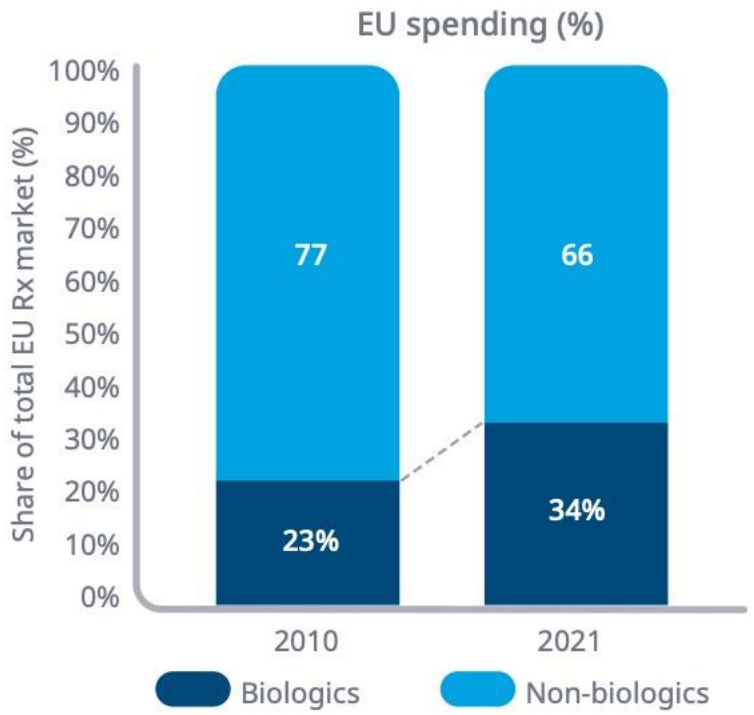
Low	**Molecular weight**	High
Simple, low potential for variation	**Structure**	Complex, high potential for variation
Chemical method producing identical molecules	**Synthesis**	Biological method producing highly similar proteins
All attributes	**Matches reference medicine in terms of**	Efficacy, PK/PD, safety and immunogenicity, as demonstrated by comprehensive preclinical and clinical comparability programme

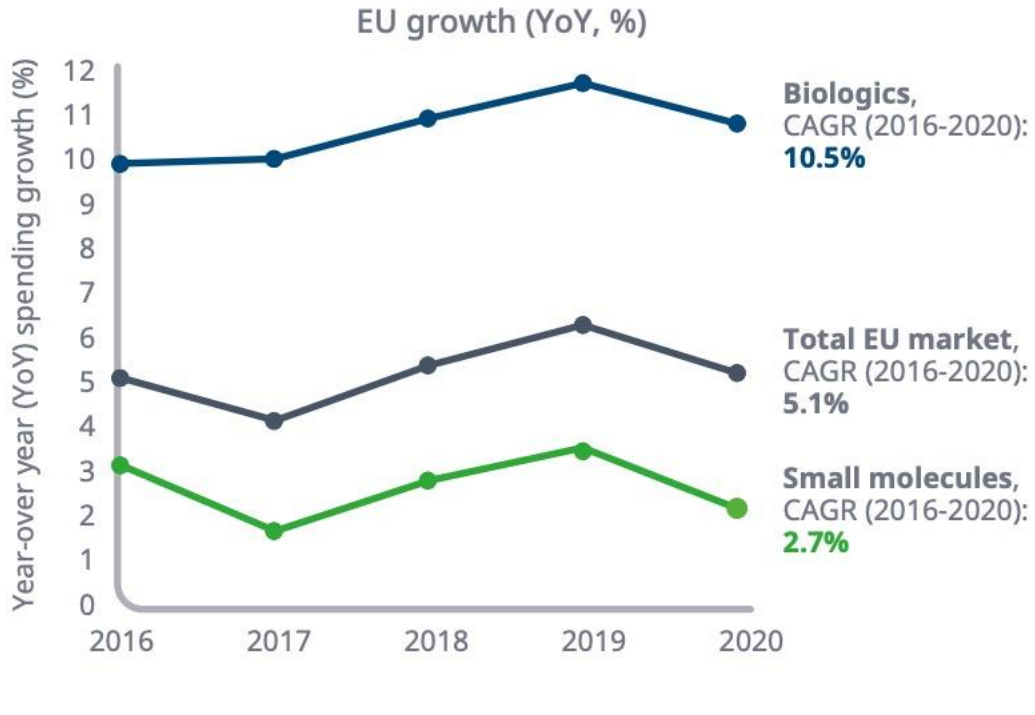
The best way to accommodate Innovation Fund

- We need to create a budget to expand access to innovation



The importance of biologics within the European pharmaceutical market





Troein et al., The Impact of Biosimilar Competition in Europe December 2021

Biosimilars approved in Europe

Source: IQVIA analysis of EMA EPAR list (last accessed November 2021)

Troein et al., The Impact of Biosimilar Competition in Europe December 2021

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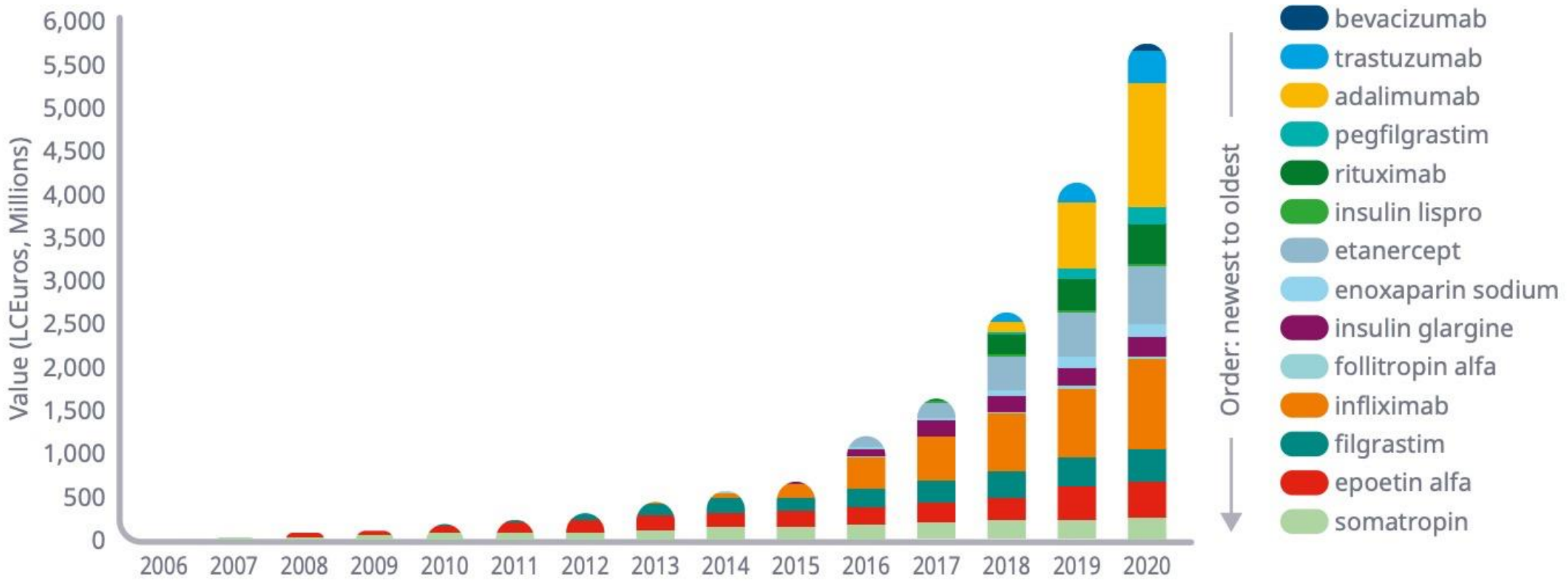
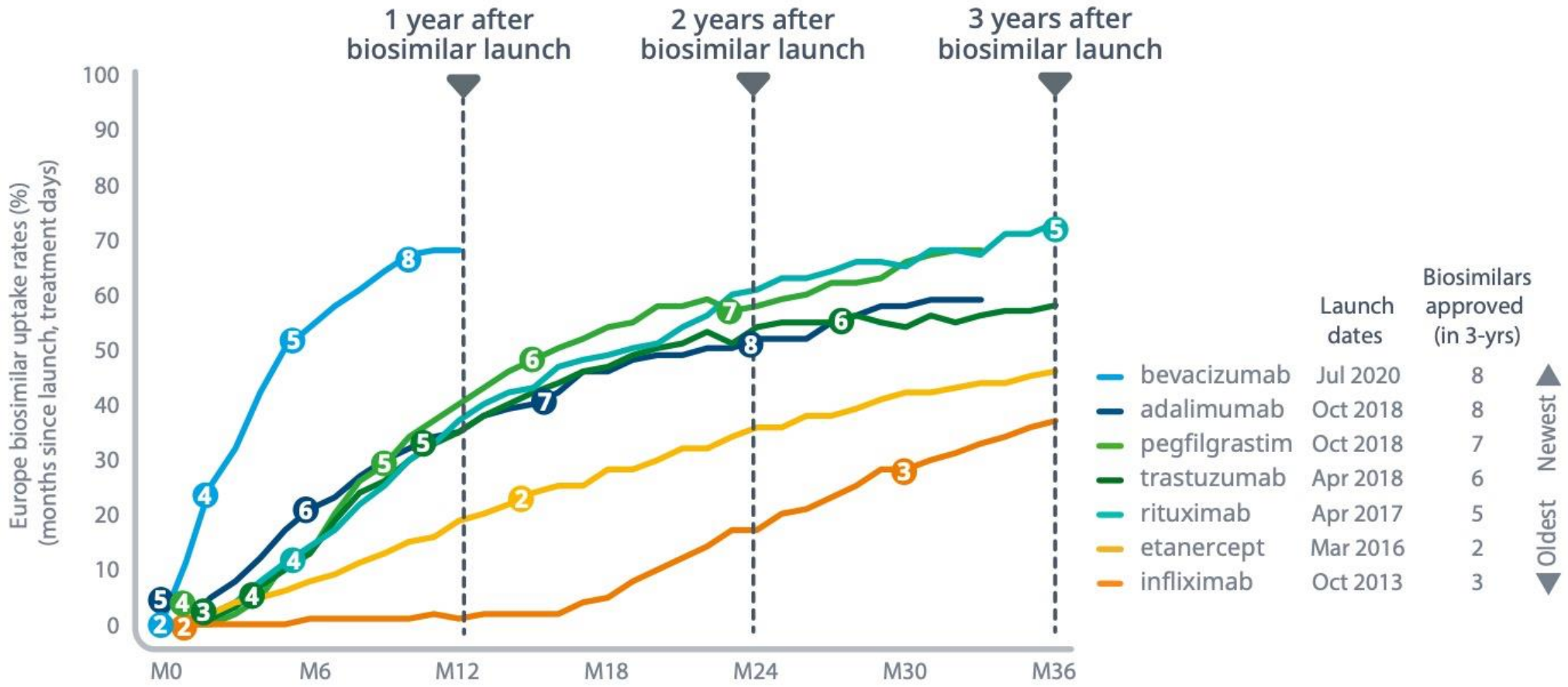
Yearly savings from biosimilar competition

Cost for post-biosimilar volume at pre-biosimilar list prices



Troein et al., The Impact of Biosimilar Competition in Europe December 2021

Increasing biosimilar uptake



Troein et al., The Impact of Biosimilar Competition in Europe December 2021

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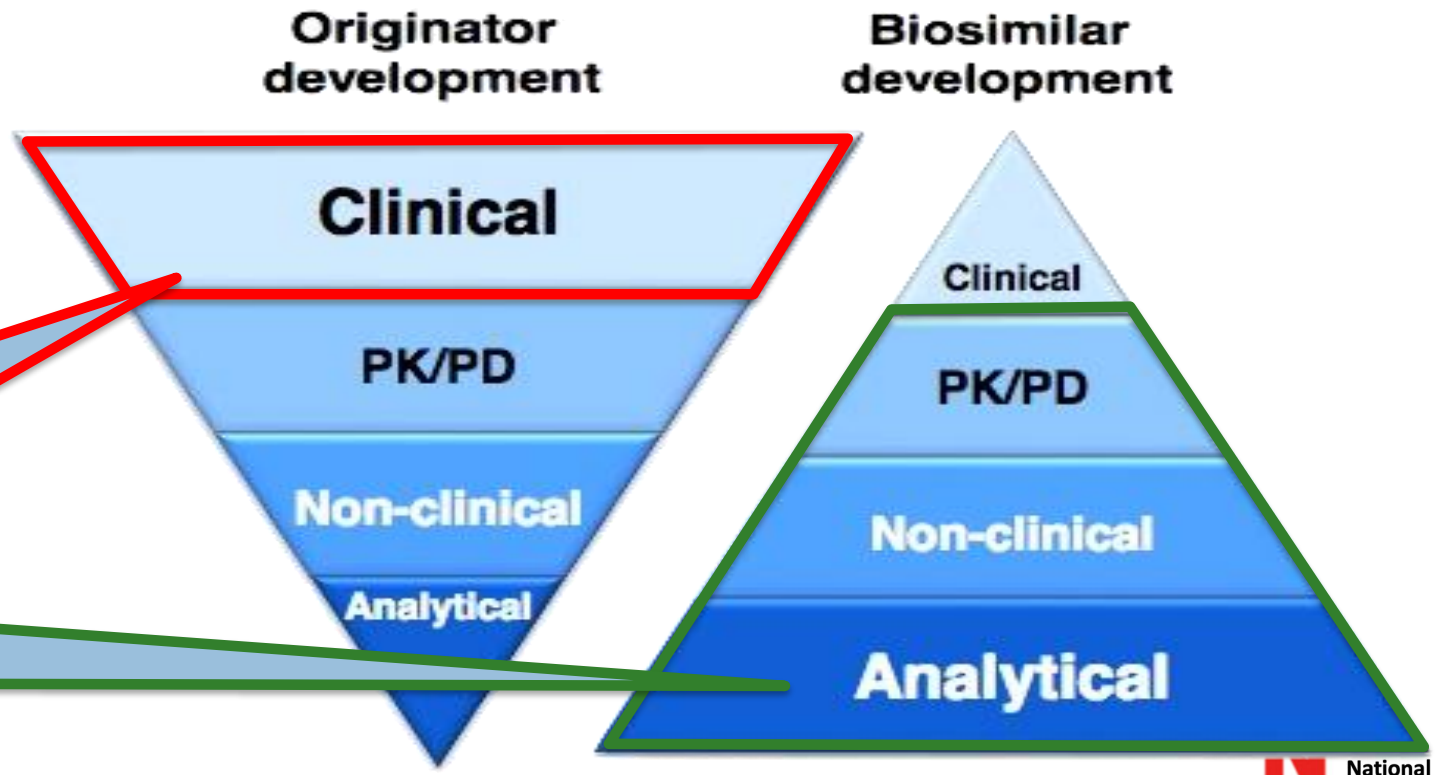
Approval of originator drugs and biosimilars is different

Physicians want big clinical trial data

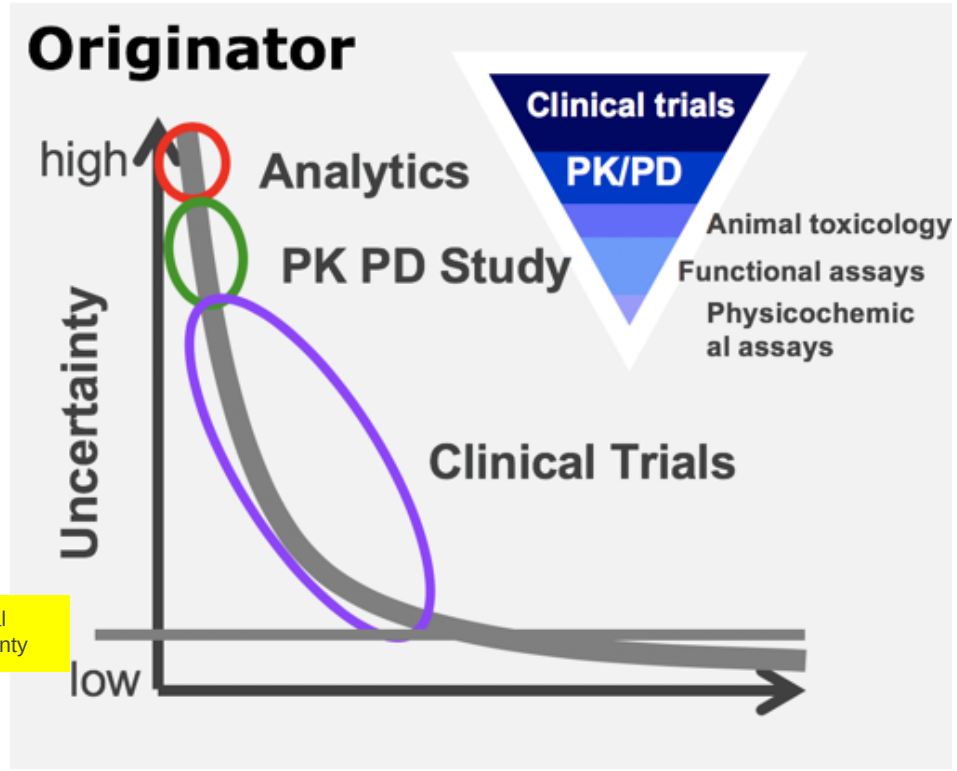
Pharmacists want pharmacological data: analytics, PK, PD & immunogenicity studies

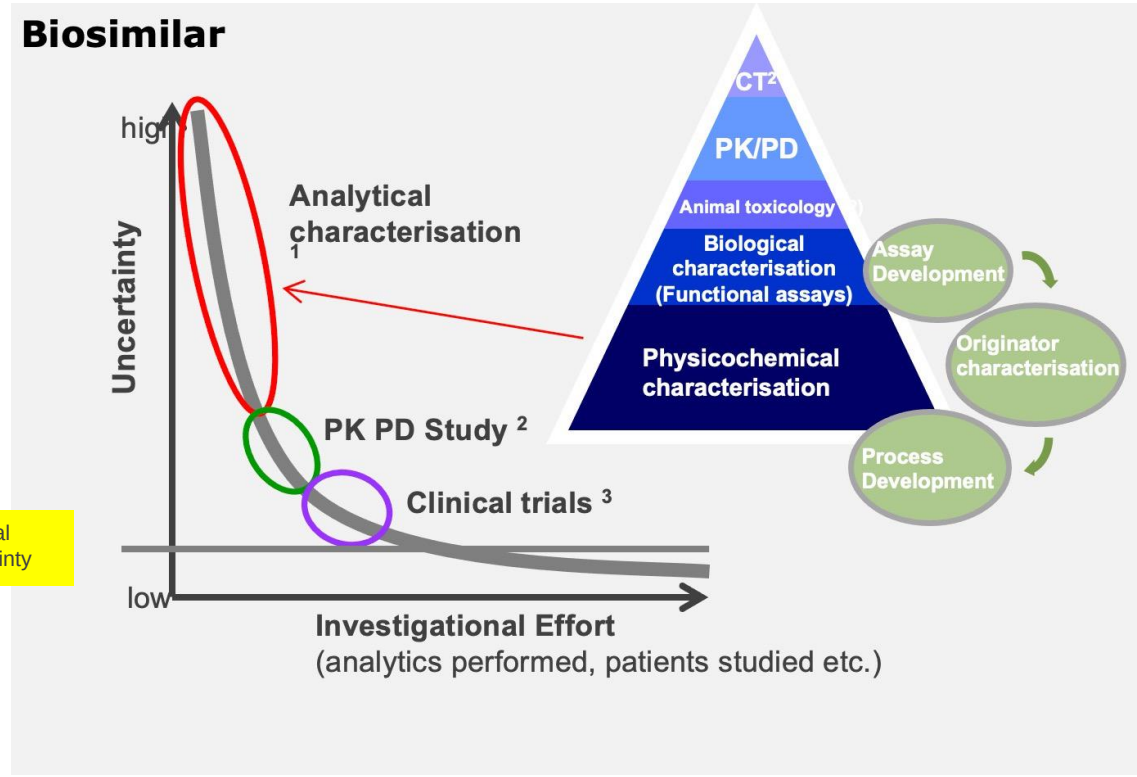
The best way to discover clinical difference for a new drug or indication

The best way to discover that versions of the same drug are not similar



Approval of originator drugs and biosimilars is different





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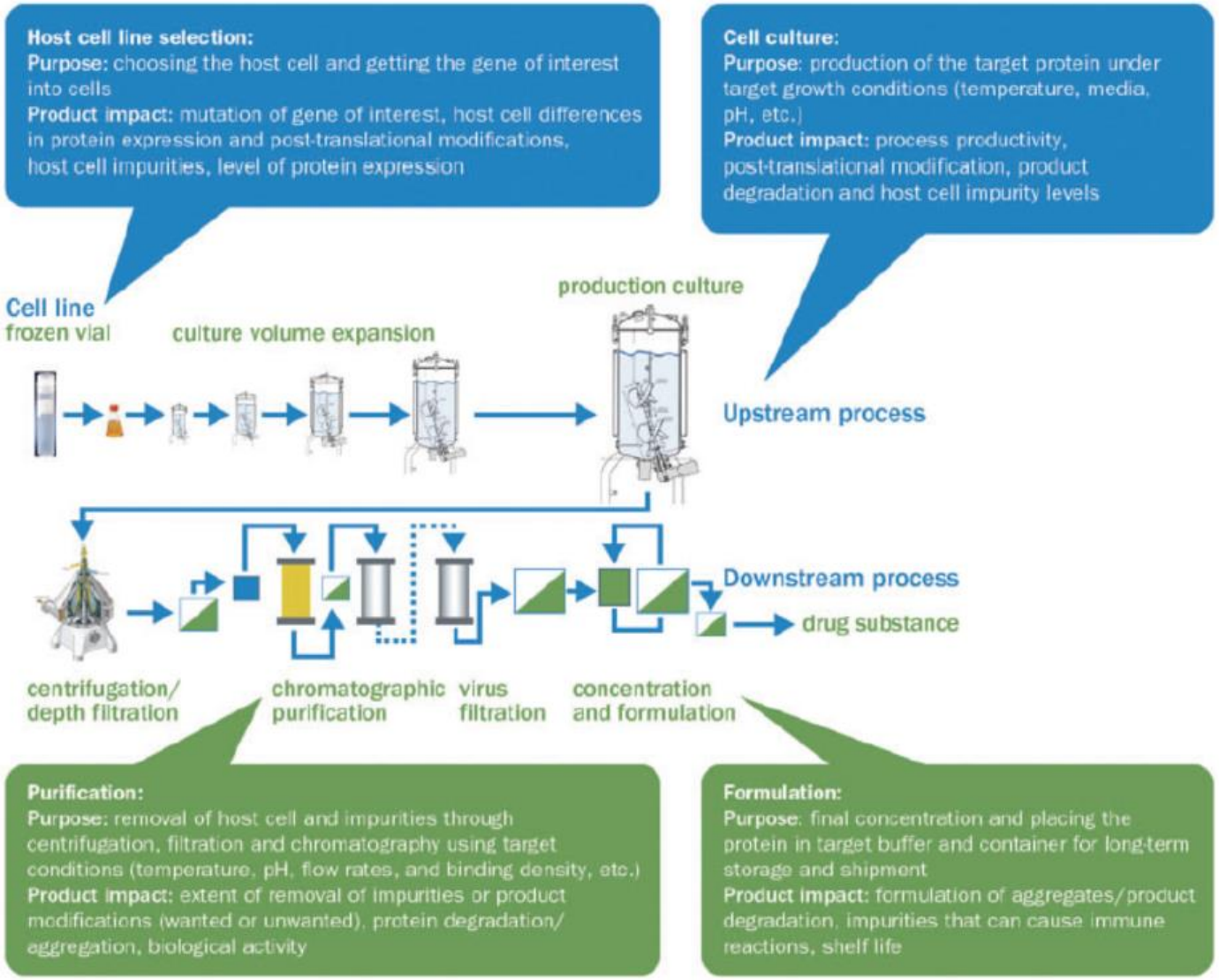
Key considerations for Phase III trial designs

	Originator	Biosimilar
Patient population	Any	Sensitive and homogeneous
Clinical design	**Superiority versus standard of care**	**Comparative versus innovator** (therapeutic equivalence studies)
Study endpoints	Clinical outcomes data (**OS & PFS**) or accepted/established surrogates	**Pharmacokinetic and Pharmacodynamic** markers; objective **response rate (RR)**
Safety	**Acceptable risk/benefit profile** versus standard of care	**Similar safety profile** to innovator
Immunogenicity	**Acceptable risk/benefit profile** versus standard of care	**Similar immunogenicity profile** to innovator
Extrapolation	**Not allowed**	**Possible** if justified

Manufactured Biologics is a complicated process



Minor changes :

– i.e. - personnel glove manufacturer

Major changes:

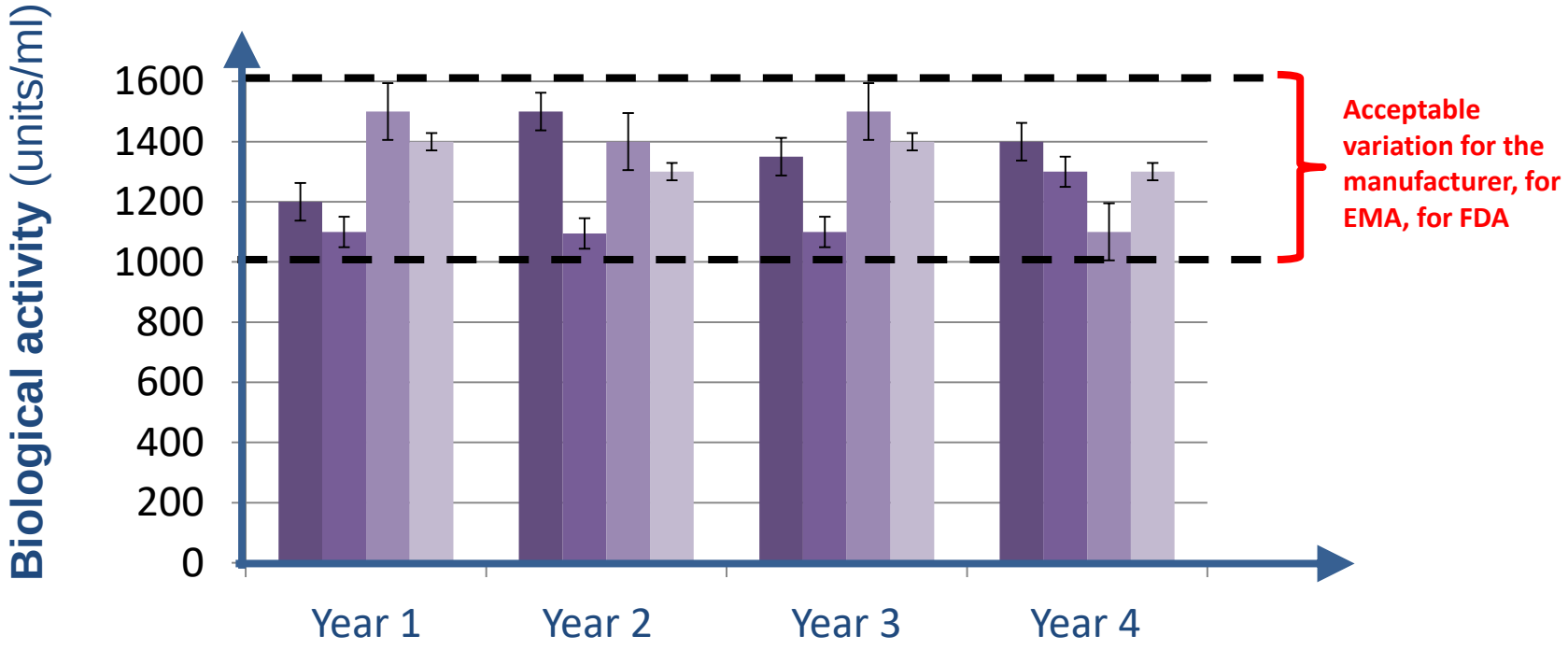
- **i.e. – filter manufacturer**

Critical changes:

- **i.e. – moving to different plant**
- **i.e. – changing the cell line**

Biologicals Are Similar But Not Identical

"Nonidenticality" is a normal principle in biotechnology.
No batch of any biologic is "identical" to the others.



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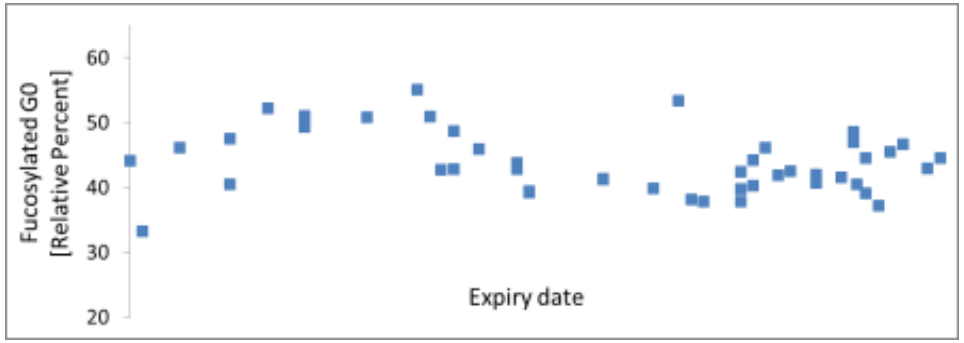
No batch of any biological is identical to the others

Batch-to-batch

- Non-identicality is a normal principle in glycosylated proteins
- No batch of any biologic is ‘identical’ to the other batches
- Variability is tightly controlled within acceptable limits

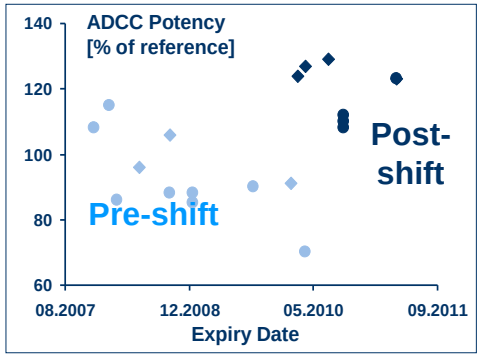
Variability of major glycan variant in commercial mAb

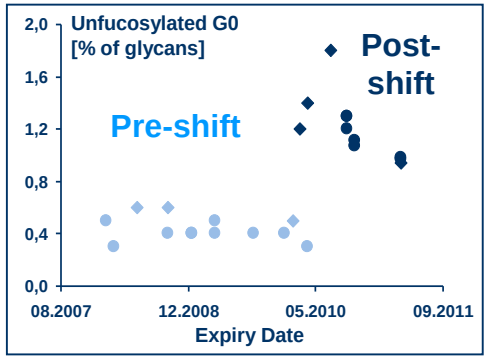


Manufacturing changes

- Manufacturing changes are made frequently
- Differences in attributes can be larger than batch-to-batch variability
- Such changes are stringently controlled by regulators and approved only if they do NOT lead to clinically meaningful differences

Variability of rituximab reference medicine before and after manufacturing change





Schiestl M, et al. *Nat Biotechnol.* 2011;29:310–2

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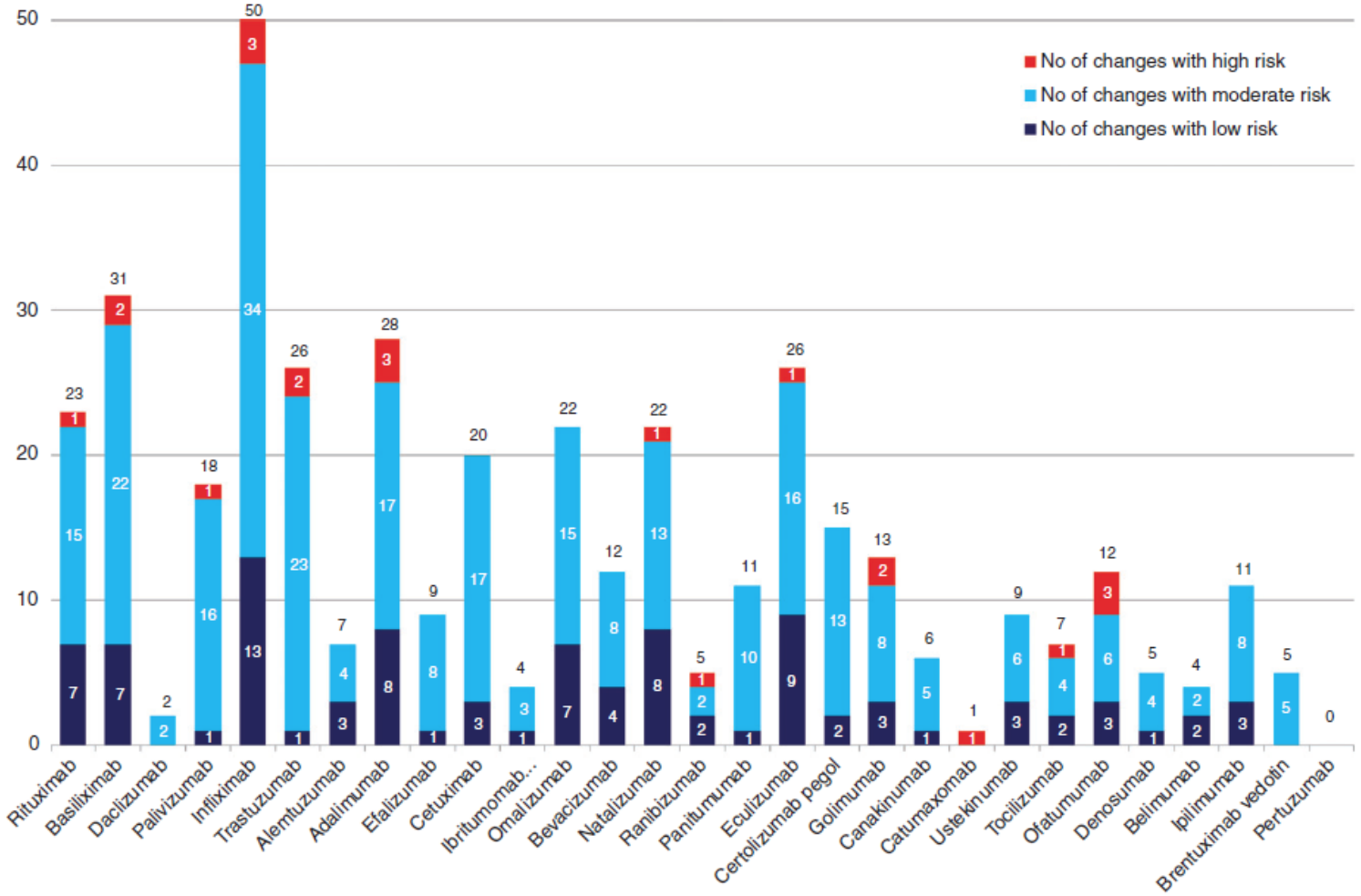
Companies may change their manufacturing processes multiple times after approval , which can impact analytical variability



Veser B. et al., Cur Med Res Op 2016; 32: 829-834

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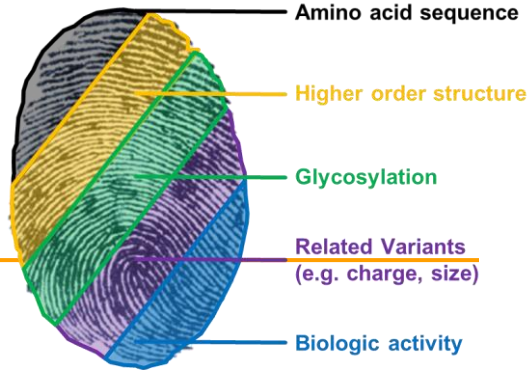
How similar are biosimilars and their reference medicines in biochemical structure?

Amino acid sequence **Primary Sequence**	**Identical**
Folding Secondary, tertiary, quaternary structure	**Indistinguishable**
Glycosylation and related substances	**Identical structures in comparable amounts** Differences are only acceptable if they are clinically not relevant
Biological functions	**Comparable**

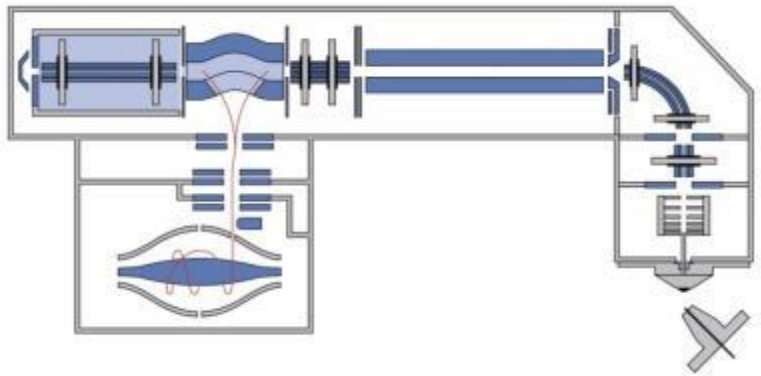


Adapted from: FDA. Guidance on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Guidance for Industry (April 2015). https://www.fda.gov/regulatory-information/search-fda-guidance-documents/scientific-considerations-demonstrating-biosimilarity-reference-product (accessed 17 June 2019).
Figure adapted from McCamish M, et al. *mAbs.* 2011;3:209–17.

Powerful tools have evolved to allow comprehensive characterization: e.g. mass spectrometry

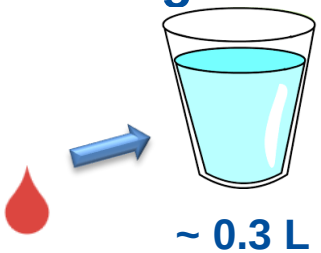
Year	MS-detection limit for peptides (pmol)
1990	100
1993	10
1997	1
2000	0.1
2003	0.01
2005	0.001
2008	0.0001
2011	0.00001

Mass spectrometry



10-million-fold increase

Analogue:

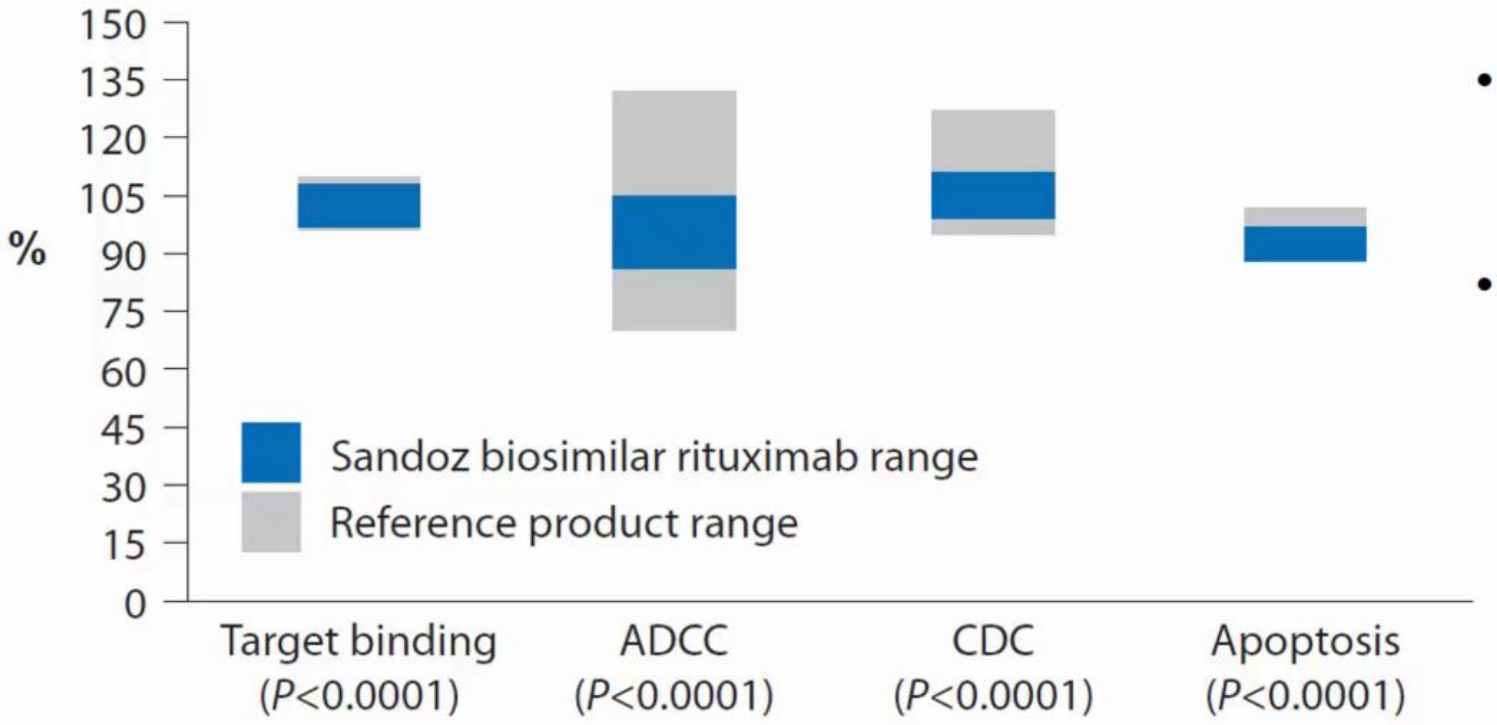


~ 0.3 L

~ 3,000,000 L

van Duijn E 2010. J Am Soc Mass Spectrom;21(6):971–8.
Adapted from Mire-Sluis T 2012, CASSS (Mass Spec) [online].
Available: http://c.ymcdn.com/sites/www.casss.org/resource/resmgr/Mass_Spec_Speaker_Slides/2012_MS_Mire-SluisTony.pdf
[accessed at March 23rd, 2016].

Biological characterisation of Sandoz Rituximab



- Potency bioassays designed to give quantitative results
- The Sandoz biosimilar rituximab is functionally indistinguishable from its reference product

The reference product range reflects the minimum and maximum value of 59 batches for the ADCC, 62 batches for the CDC bioassay, 48 batches for target binding and 7 batches for the apoptosis bioassay, which was developed later. The Sandoz biosimilar rituximab range reflects the minimum and maximum value of 11 clinic batches for binding, ADCC and CDC and 5 batches for the apoptosis assay
*Assessed using the two-sided test procedure (TOST) with bioequivalence limits of 0.8–1.25

Visser et al. BioDrugs 2013;27:495–507. ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity;

First 2 Rituximab Biosimilars approved by EMA

Sandoz rituximab (1054 patients)

Study	Design	Indication	Primary endpoint	N	Status
JP-trial	Phase I Open-label Single-arm	Indolent LTB NHL	Safety and PK of SDZ-RTX	6	**Completed** NCT01933516
ASSIST-RA	Phase II RCT (1:1:1) Double-blind	RA	PK equivalence between SDZ-RTX and Ref-RTX	312	**Completed** Published[1]
ASSIST-FL	Phase III RCT (1:1) Double-blind	Advanced FL	Therapeutic equivalence between SDZ-RTX and Ref-RTX-EU	629	**Study ongoing** Published[2]
ASSIST-RT	Phase III RCT (1:1) Double-Blind	RA	Safety and immunogenicity	107	**Completed** Published[3]

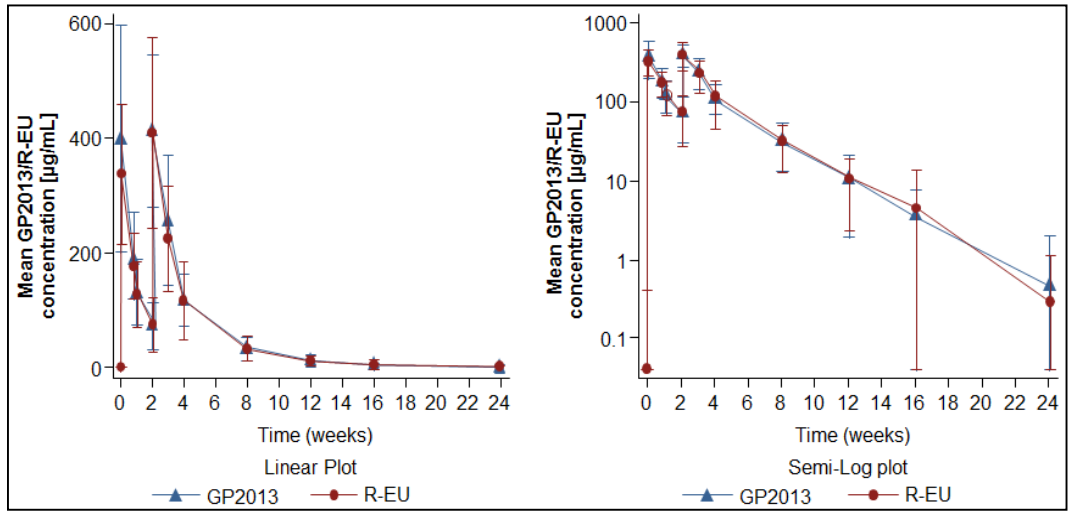
CT-P10 (982 patients)

Study	Design	Indication	Primary endpoint	N	Status
1.1	Phase I RCT (2:1) Double-blind	RA	PK equivalence between CT-P10 and Ref-RTX	154	**Completed** Published[4,5]
1.3 (1.1 follow-on study)	Phase I Open-label Single-arm	RA	Long-term efficacy and safety of CT-P10	58	**Completed** Published[6]
1.2	Phase I Open-label Single-arm	DLBCL	Initial evidence of CT-P10 safety	N/A	**Terminated** recruitment difficulties[7,8]
3.2	Phase III RCT (1:1:1) Double-blind	RA	PK and therapeutic equivalence between CT-P10 and Ref-RTX	372	**Study ongoing** Published[9]
3.3	Phase I/III RCT (1:1) Double-blind	Advanced FL	PK equivalence and therapeutic non-inferiority between CT-P10 and Ref-RTX-US	140	**Study ongoing** Published[10]
3.4	Phase III RCT (1:1) Double-Blind	LTB FL	Therapeutic equivalence between CT-P10 and Ref-RTX	258	**Recruiting**[11]

Coiffier et al., Lancet Haematol 2017, Jurczak et al., Lancet Haematol 2017, Ogura et al., Lancet haematol 2018

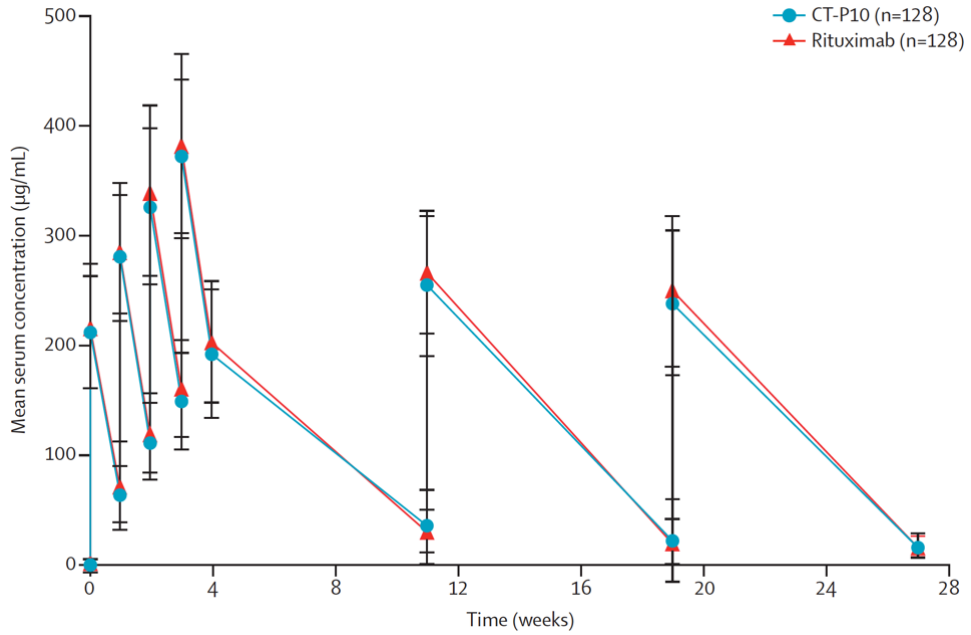
Pharmacokinetics - ($AUC_{(0\text{-}inf)}$)- (PAS)

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment



Smolen J et al., Ann Rh Dis. 2017

CT-P10 3.4 FL



Ogura et al Lancet Haematol 2018

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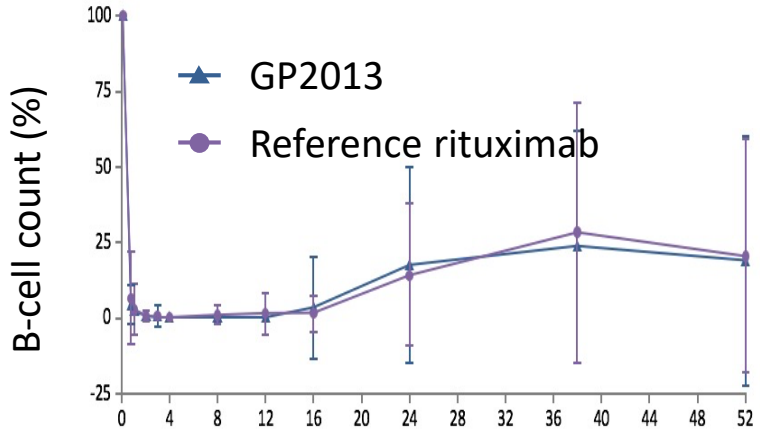
Pharmacodynamics - peripheral B cell depletion

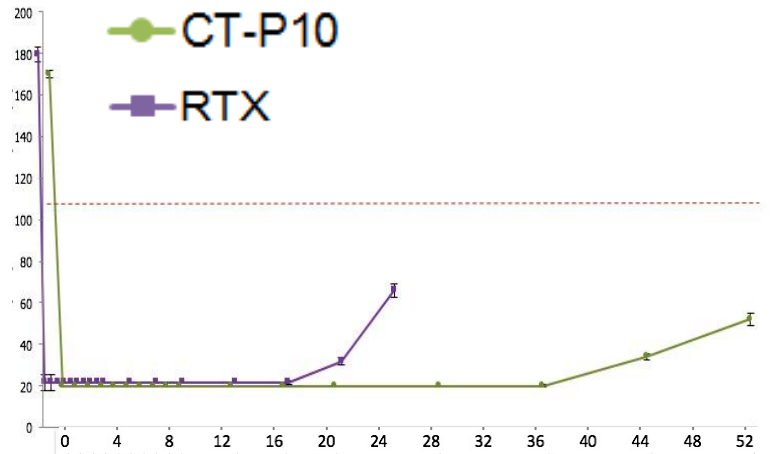
ASSIST-RA
Affordable Efficacy & Safety from Rituximab Biosimilar Treatment

Geometric mean ratio in $AUEC_{0-14d}$
1.019 (95% CI: 0.997, 1.042)



CT-P10 3.2 RA

Median (±SE) B-cell Kinetics (cells/µL)



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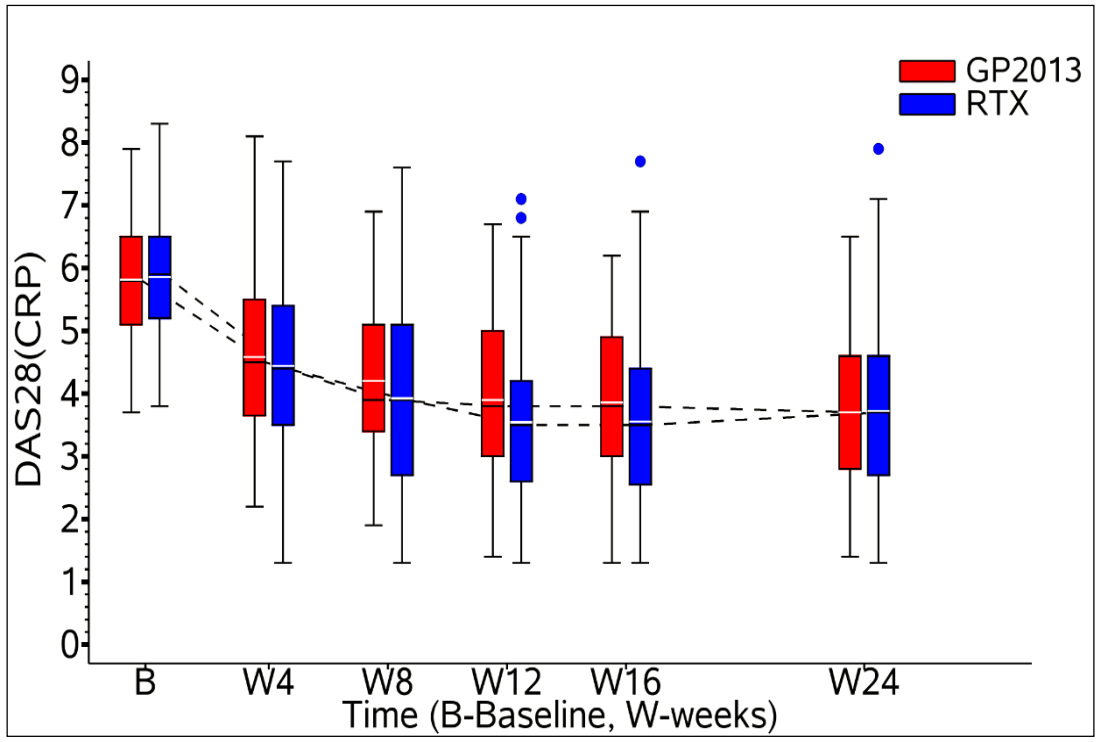
Efficacy DAS (Disese Activity Score)

ASSIST-RA
Affordable Efficacy & Safety from Rituximab Bioimilar Treatment

CT-P10 3.2 RA



Parameters TreMedian (±SE) B-cell Kinetics (cells/µL)	n	Adjusted Mean (SE)	Estimate of Treatment Difference (95% CI)
DAS28 (CRP) – Efficacy Primary endpoint			
CT-P10	139	-2.14 (0.177)	
US/EU-RTX	196	-2.09 (0.176)	-0.29 -0.05 0.20
DAS28 (ESR)			
CT-P10	140	-2.41 (0.182)	
US/EU-RTX	196	-2.35 (0.182)	-0.31 -0.06 0.19

-0.6 -0.3 0 0.3 0.6

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GP13-302
ASSIST-RT

GP13-302 clinical trial assessing AE in RA patients treated previously with originator Rituximab

	GP 2013 (N)	MabThera (N)	Total (N)
No of treated patients	53	54	107
Anaphylactic Reactions	0	**1**	1
Hypersensitivity Reactions	5	**6**	11
Immunogenicity	0	**1**	1
Infusion-Related Reactions	6	**10**	16
SAE	0	**4**	4
AE	19	**21**	40

www.clinicaltrials.gov/ct2/show/results/NCT02514772

Study rationale in FL

- Studies were **designed to confirm non-inferior clinical effectiveness** of biosimilar as compared to originator rituximab in a sensitive population
- **Follicular lymphoma** was chosen as the most appropriate indication as the disease **has a more homogeneous nature** amongst the approved oncology indications of rituximab
- Further, the combination **R-CVP was considered the most sensitive treatment option**, as rituximab had shown the largest additive treatment effect to a chemotherapy backbone treatment in the combination with CVP
- Immunochemotherapy with Rituximab **remains the current standard of care** for previously untreated patients , the combination regimen increases the **RR** and prolongs both PFS and **OS**

Jurczak W, et al. Lancet Haematol 2017
Coiffier B ,et al. Lancet Haematol 2017

Comparison of study design – phase III studies in advanced FL

	ASSIST-FL[1] Phase III	CT-P10 3.3[2] Phase III
Number of patients randomized	N=627	N=140 (N=121 in part 1)
Patient characteristics	• Advanced FL (Ann Arbor stage III–IV) • WHO grade 1-3a (confirmed by central pathological testing)	• Advanced FL (Ann Arbor stage III–IV) • WHO grade 1-3a (based on local laboratory review)
Induction therapy	R-CVP (8 x 3-week cycles)	R-CVP (8 x 3-week cycles)
	IV cyclophosphamide (750 g/m^2) on Day 1	IV cyclophosphamide (750 g/m^2) on Day 1
	IV vincristine (1.4 mg/m^2) on Day 1	IV vincristine (1.4 mg/m^2) on Day 1
	Oral prednisone (100 mg) on Days 1–5	Oral prednisone/prednisolone (40 mg/m^2) on Days 1–5
	IV SDZ-RTX or Ref-RTX-EU (375 mg/m^2) on Day 1	IV CT-P10 or Ref-RTX-US (375 mg/m^2) on Day 1
Maintenance therapy	IV SDZ-RTX or Ref-RTX-EU (375 mg/m^2) Every 3 months for 2 years (every 2 months in Italy)	IV CT-P10 or Ref-RTX-US (375 mg/m^2) Every 2 months for 2 years
Primary objective(s)	• To demonstrate equivalent efficacy between SDZ-RTX and Ref-RTX-EU in terms of centrally assessed overall response (CR+PR) at 24 weeks	• Part 1 - To demonstrate PK equivalence between CT-P10 and Ref-RTX-US in terms of AUC_{tau} and C_{maxSS} over induction Cycle 4 (Weeks 9–12) • Part 2 - To demonstrate non-inferior efficacy of CT-P10 compared with Ref-RTX-US in terms of centrally assessed overall response (CR+CRu+PR) at 24 weeks
Secondary objectives	PK: C_{max}, C_{trough}, AUC_{0-21d}, AUC_{all} PD: Median B-cell count, AUEC Efficacy: PFS, OS Safety and immunogenicity	PK: C_{max}, C_{trough}, C_{av}, T_{max}, V_{SS}, $T_{1/2}$, MRT, PTF PD: Median B-cell count Efficacy: PFS, TTP, TTF, DFS, OS Safety and immunogenicity

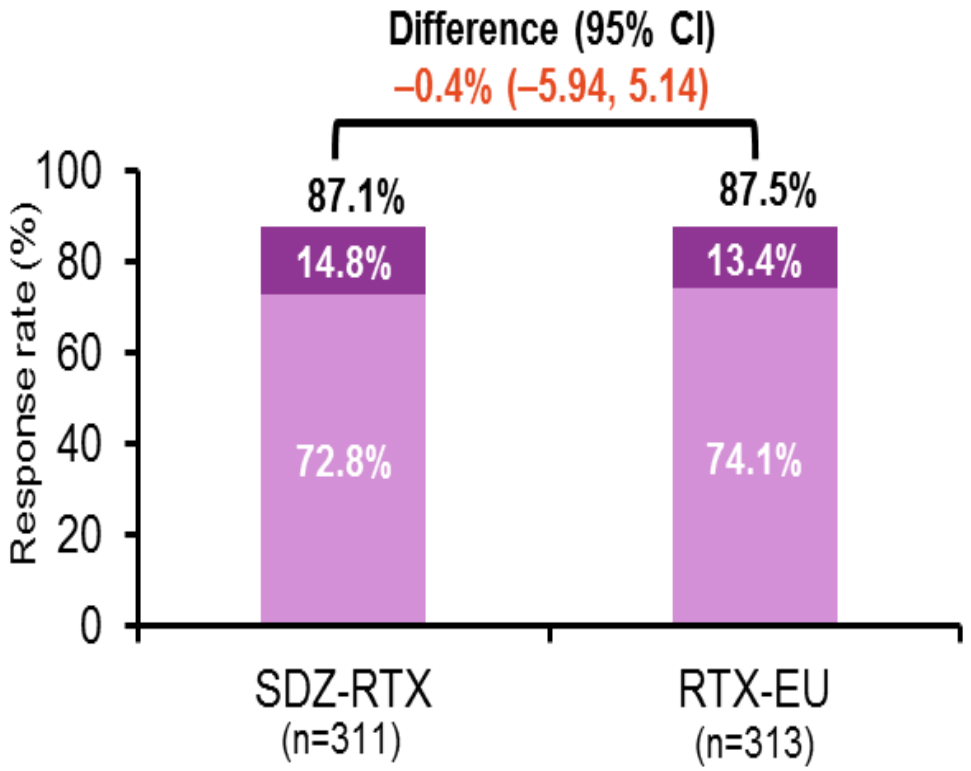
Jurczak et al, Lancet Haematol 2017
Coiffier et al, Lancet Haematol 2017

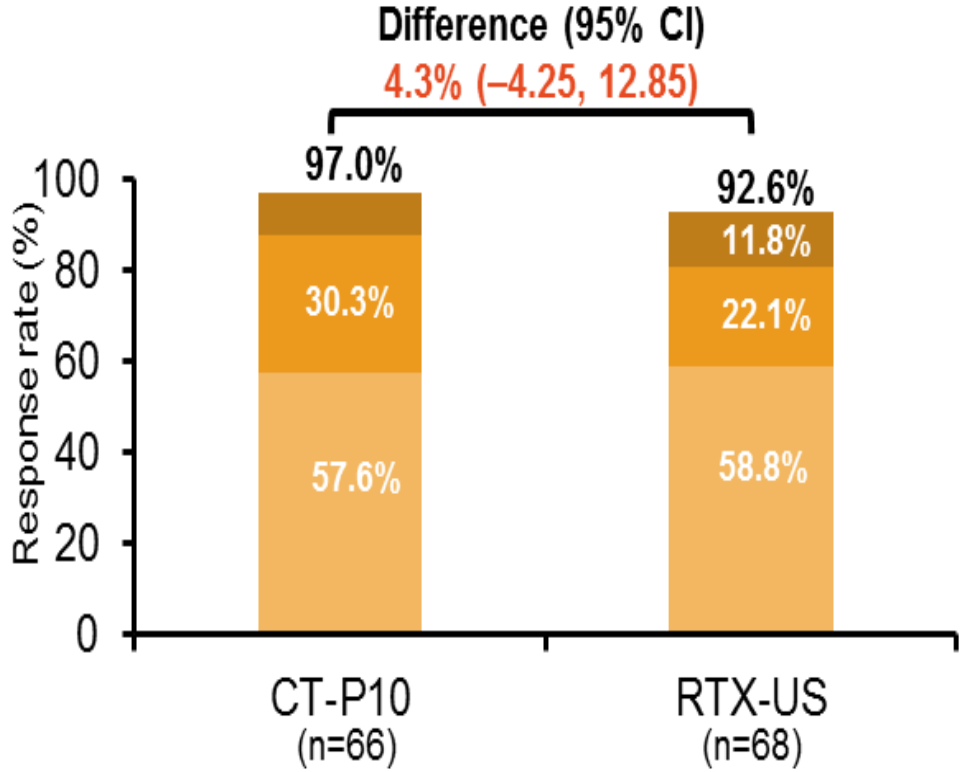
Patient demographics and baseline characteristics - phase III studies in advanced FL

		ASSIST-FL[1] (N=627)		CT-P10 3.3[2] (N=140)	
		SDZ-RTX (N=312)	Ref-RTX-EU (N=315)	CT-P10 (n=70)	Ref-RTX-US (N=70)
Age, years		57.5 (SD: 11.86)	56.4 (SD: 11.72)	57.0 (IQR: 45–66)	58.5 (IQR: 47–66)
Gender – female, n (%)		181 (58)	169 (54)	40 (57)	37 (53)
FLIPI score, n (%)	0-1	30 (10)	35 (11)	8 (11)	6 (9)
	2	106 (34)	103 (33)	25 (36)	21 (30)
	>3	176 (56)	177 (56)	37 (53)	43 (61)
ECOG performance score, n (%)	0	179 (57)	175 (56)	44 (63)	47 (67)
	1	125 (40)	123 (39)	25 (36)	22 (31)
	2	5 (2)	13 (4)	1 (1)	1 (1)
	Missing	3 (1)	4 (1)	0	0
Bulky disease (tumour > 7cm), n (%)		44 (14)	56 (18)	11 (16)	14 (20)

Jurczak et al, Lancet Haematol 2017
Coiffier et al, Lancet Haematol 2017

Primary efficacy results – phase III studies in advanced FL





Jurczak et al, Lancet Haematol 2017
Coiffier et al, Lancet Haematol 2017

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Safety and immunogenicity results - phase III studies in advanced FL

	ASSIST-FL[1] (N=627)		CT-P10 3.3[2] (N=140)	
	SDZ-RTX (N=312)	Ref-RTX-EU (N=315)	CT-P10 (N=70)	Ref-RTX-US (N=70)
Any adverse event (AE)	289 (92.6)	288 (91.4)	58 (82.9)	56 (80.0)
Grade 3 neutropenia	48 (15.4)	51 (16.2)	15 (21)	7 (10)
Serious AE	71 (22.8)	63 (20.0)	16 (22.9)	9 (12.9)
Infusion-related reaction	41 (13.1)	37 (11.7)	16 (22.9)	17 (24.3)
Deaths	4 (1.3)	7 (2.2)	1 (1.4)	0
Anti-drug antibodies	5/268 (2)	3/283 (1)	3 (4)	2 (3)

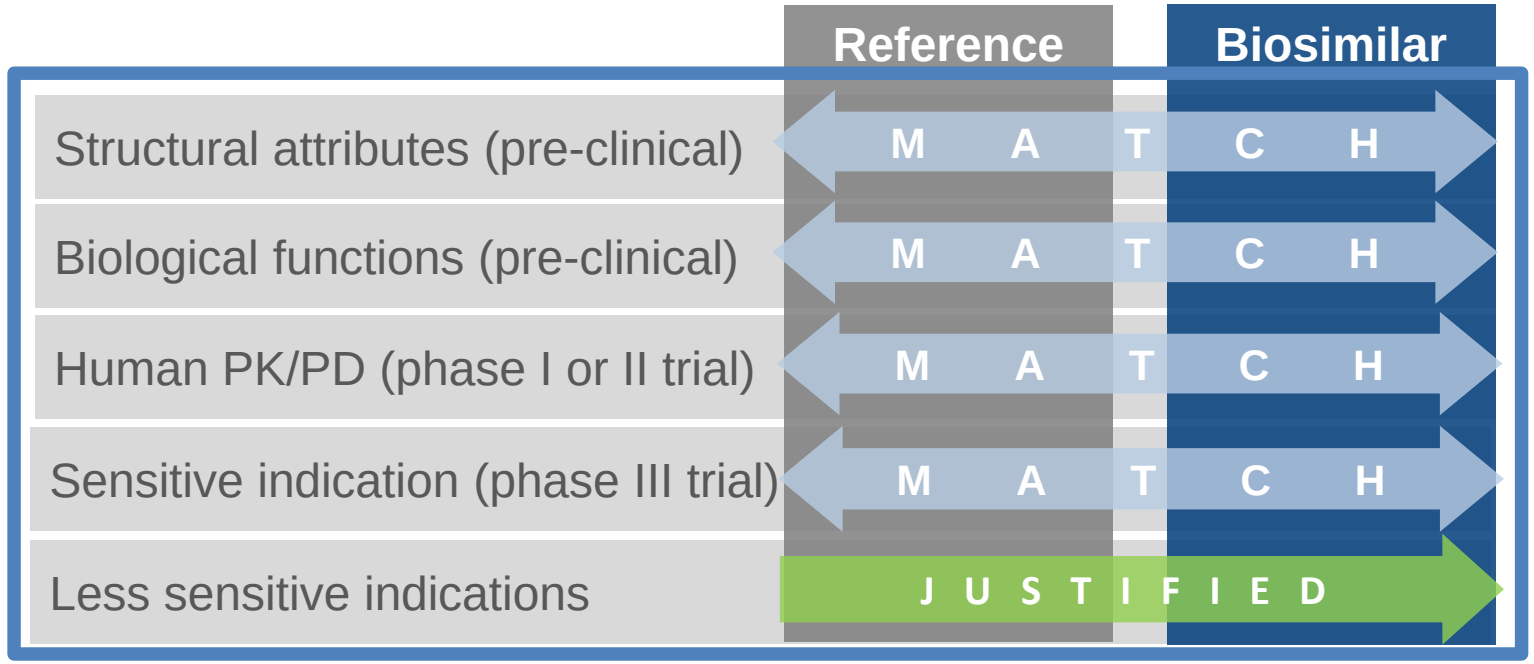
Jurczak et al, Lancet Haematol 2017
Coiffier et al, Lancet Haematol 2017

Rituximab Biosimilars approved by EMA

Product name	Manufacturer	Therapeutic area	Authorization date
Blitzima	Celltrion	NHL	13 Jul 2017
Rixathon	Sandoz	CLL, NHL Microscopic polyangiitis, RA, Wegener granulomatosis	15 Jun 2017
Riximyo	Sandoz	CLL, NHL Microscopic polyangiitis, RA, Wegener granulomatosis	15 Jun 2017
Ruxience	Pfizer	CLL, NHL, Granulomatosis with polyangiitis, Microscopic polyangiitis, RA, Pemphigus vulgaris	1 Apr 2020
Truxima	Celltrion	CLL, NHL, Granulomatosis with polyangiitis, Microscopic polyangiitis, RA	17 Feb 2017

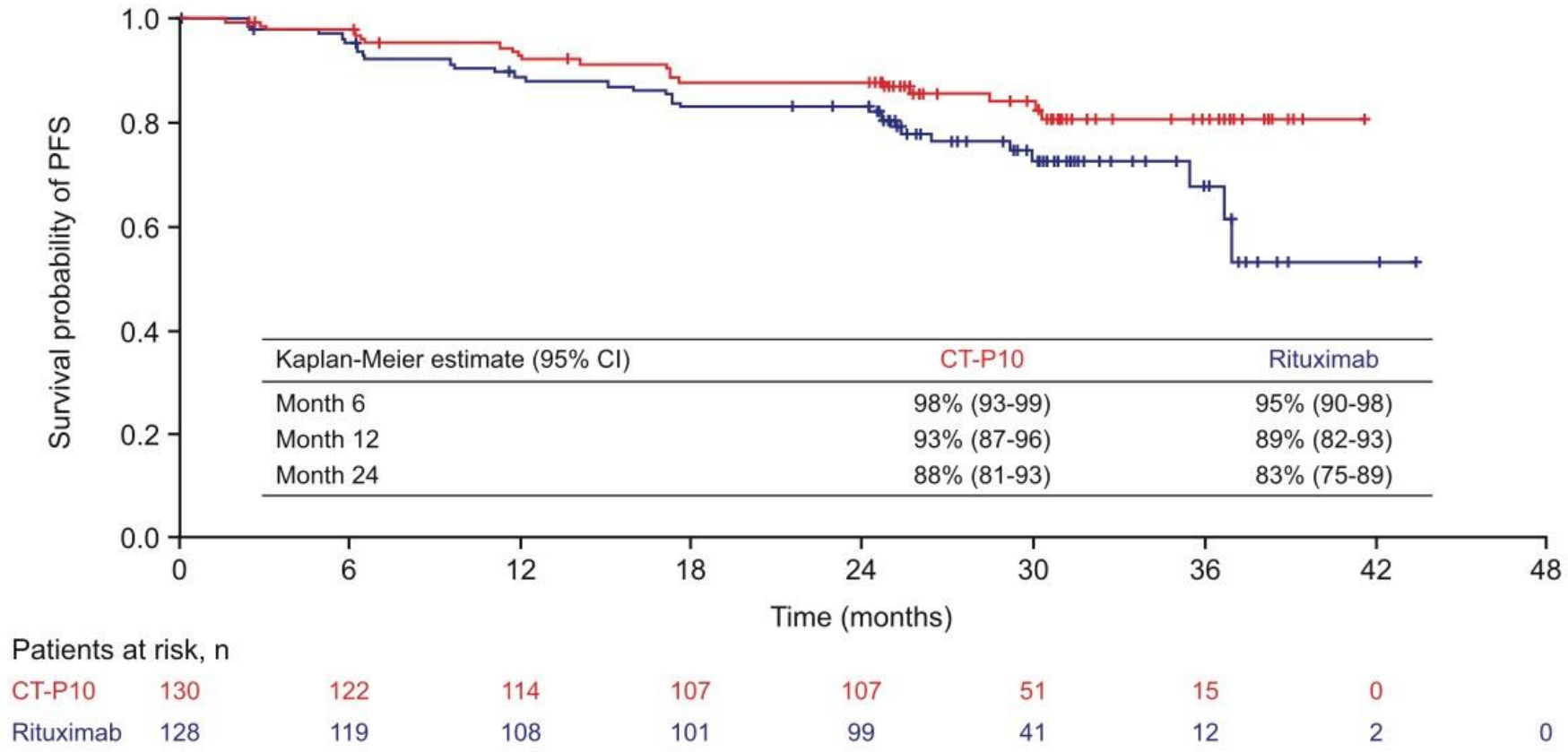
Rituximab Biosimilar / Company	Published supporting data						Approved/status
	Physico-chemical	Functional	Pre-clinical data	Clinical data			
				Indolent NHL/FL	DLBCL	RA	
Biosimilars (approved by EMA or FDA)							
GP2013	Sandoz (Germany)	✓	✓	✓	✓	×	✓	Europe (2017)
CT-P10	Celltrion (S. Korea)	✓	✓	×	✓	×	✓	Europe (2017); US (2019)
PF-05280586	Pfizer (US)	✓	✓	✓	✓	×	✓	Europe (2020)
Biosimilars but under clinical development (not yet approved by the EMA or FDA)							
RTXM83	mAbxience (Spain)	✓	✓	✓	×	✓	×	Phase III (approved in Brazil)
ABP 798	Amgen (US)	✓	✓	×	×	×	×	Phase III
Mabion CD20	Mabion (Poland)	×	×	×	×	×	×	Submitted to EMA (2018)
SAIT101	Archigen (UK)	×	×	×	×	×	×	Phase III
Biomimics (distributed in some countries, but not approved to the regulatory standards of EMA or FDA)							
BCD-020	Biocad (Russia)	×	×	×	✓	×	✓	Russia (2014)†
Reditux	Dr. Reddy's (India)	×	×	×	×	✓	×	India (2007)‡

Extrapolation is based on the entire similarity exercise



PD, pharmacodynamics; PK, pharmacokinetics
Kurki P, et al. J Crohns Colitis 2014;8:258; Weise M, et al. Blood 2014;124:3191–6; Weise M, et al. Blood 2012;120:5111–17; Sandoz-generated/owned figure (November 18 2014).

CT-P10 vs Rituximab in Untreated Low-Tumor-Burden FL



Kwak et al., Clin.Lymph, Myeloma and Leuk. 2021

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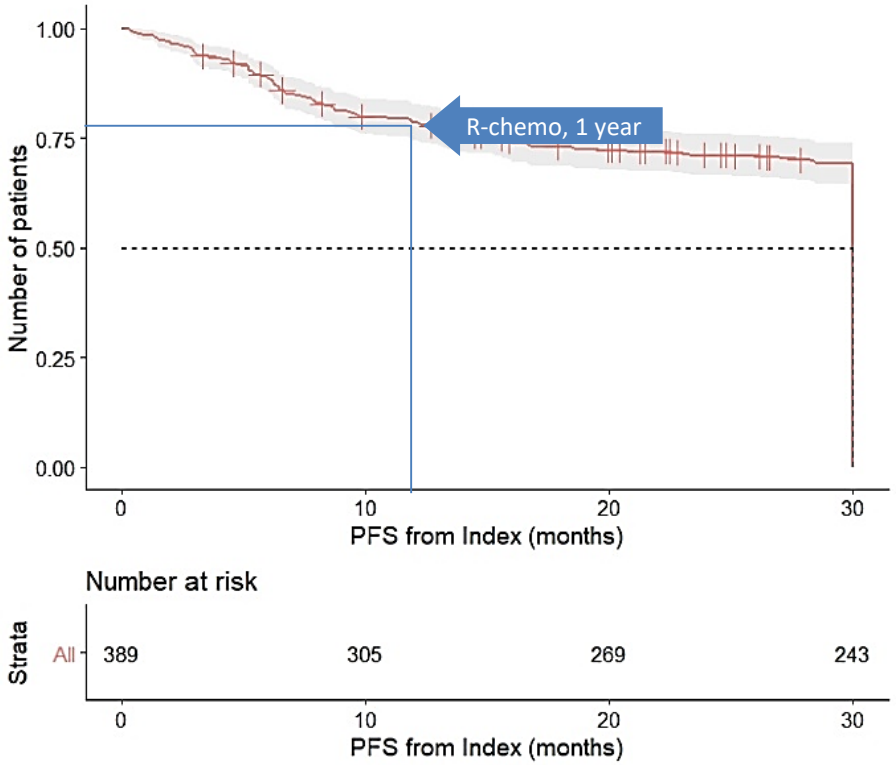
CT-P10 vs Rituximab in Untreated Low-Tumor-Burden FL

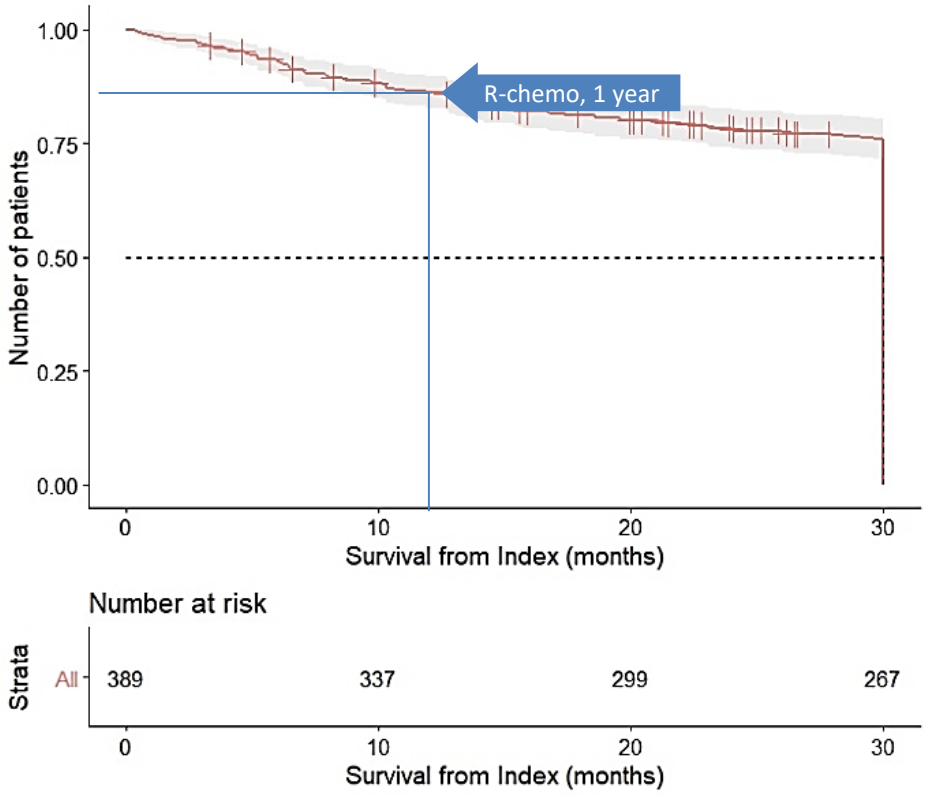
	CT-P10 ($n = 130$)	Rituximab ($n = 128$)
Total number of TEAEs	593	591
Patients with ≥ 1 TEAE	114 (88)	104 (81)
Study drug-related	74 (57)	64 (50)
Patients with ≥ 1 TEAE due to infections and infestations	59 (45)	53 (41)
Study drug-related	21 (16)	15 (12)
Patients with ≥ 1 TEAE leading to permanent study drug discontinuation	9 (7)	2 (2)
Study drug-related	3 (2)	2 (2)
Patients with ≥ 1 TEAE due to IRRs	42 (32)	39 (30)
Patients with ≥ 1 TEAE due to PML	0	0
Patients with ≥ 1 TESAE	14 (11)	14 (11)
Study drug-related	3 (2)	4 (3)

Kwak et al., Clin.Lymph, Myeloma and Leuk. 2021

DLBCL patients treatmed with CT-P10 as part of their standard clinical care in five European countries

PFS





Bishton M et al., EHA 2021, Abstract #EP529.

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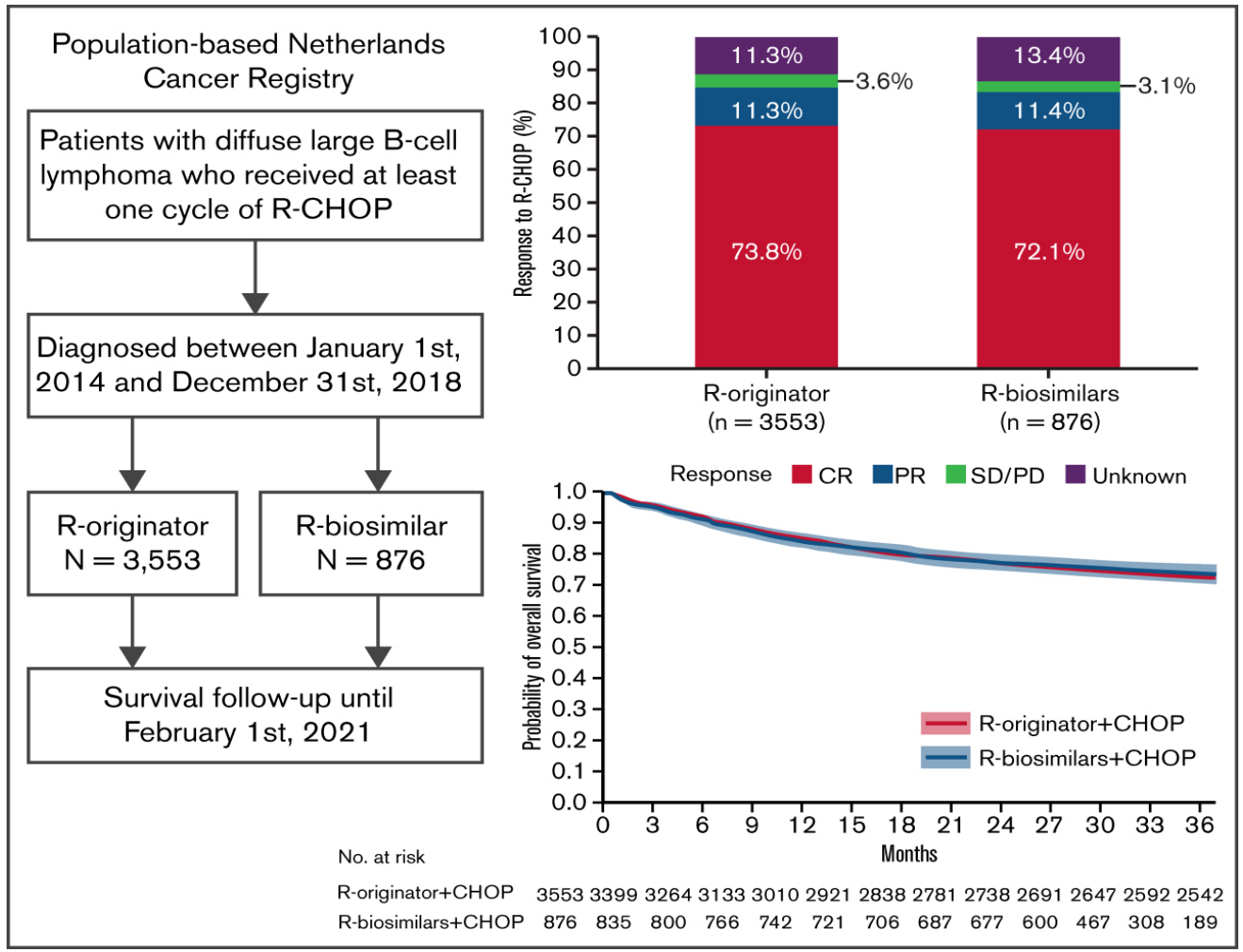
Impact of rituximab biosimilars on OS in DLBCL

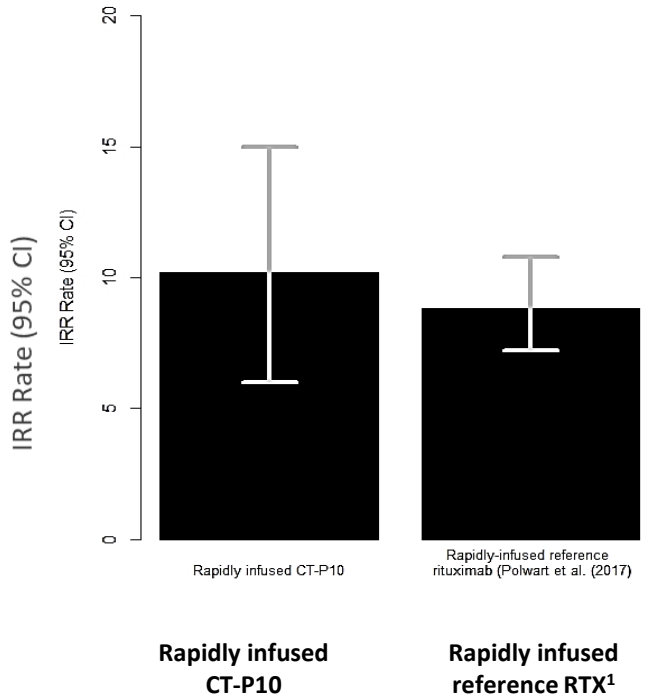


A Dutch population-based study

Mirian Brink et al Blood Adv 2021

Rapid Infusion Study of Rituximab Biosimilar

IRR rate	RAPID	Polwart et al., 2017[1]
IRR rate (%)	**10.2**	**8.8**
95% CI	6 – 15%	7.2 – 10.8%
p-value	Reference	0.45
Summary statistics		
Study type	PASS	Meta-analysis
n	196	2,472
Patients	NHL, CLL	Haematological malignancies



Bishton M et al., EHA 2021

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Conclusions:

- **Rituximab biosimilars are good quality MoAb** with a safety and efficacy profile identical to their originator

- Their similarity to Rituximab was determined by extensive pre-clinical analyses, and finally confirmed by clinical trials, with **over 3000 participating patients**

- **Biosimilar for Biobetter:** over 500 millions Euro saved every year in Europe, after introducing Rituximab biosimilars, allows to finance the innovation found

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