Biosimilar market in context

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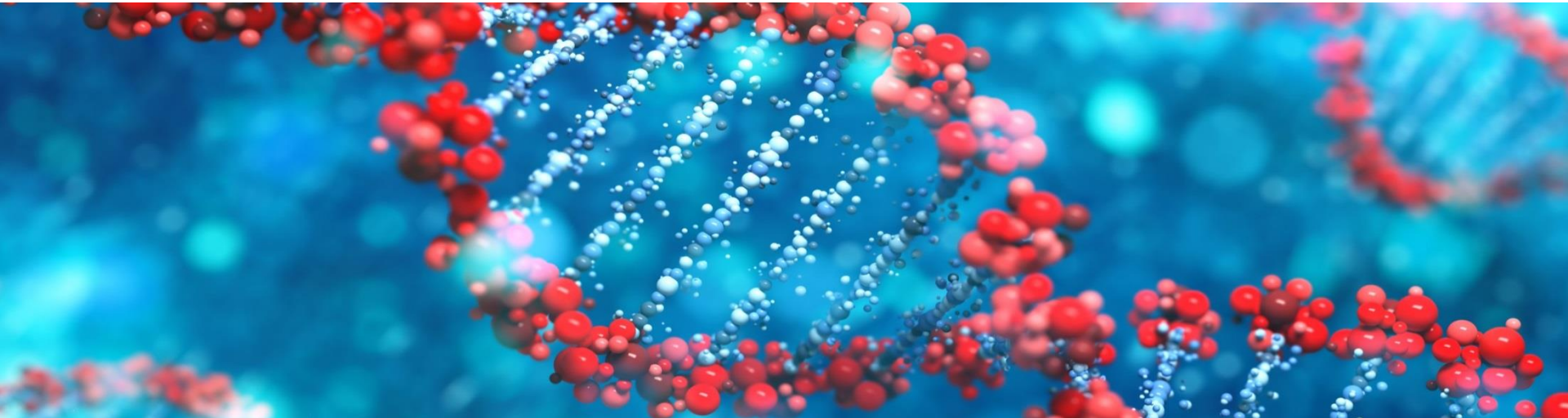
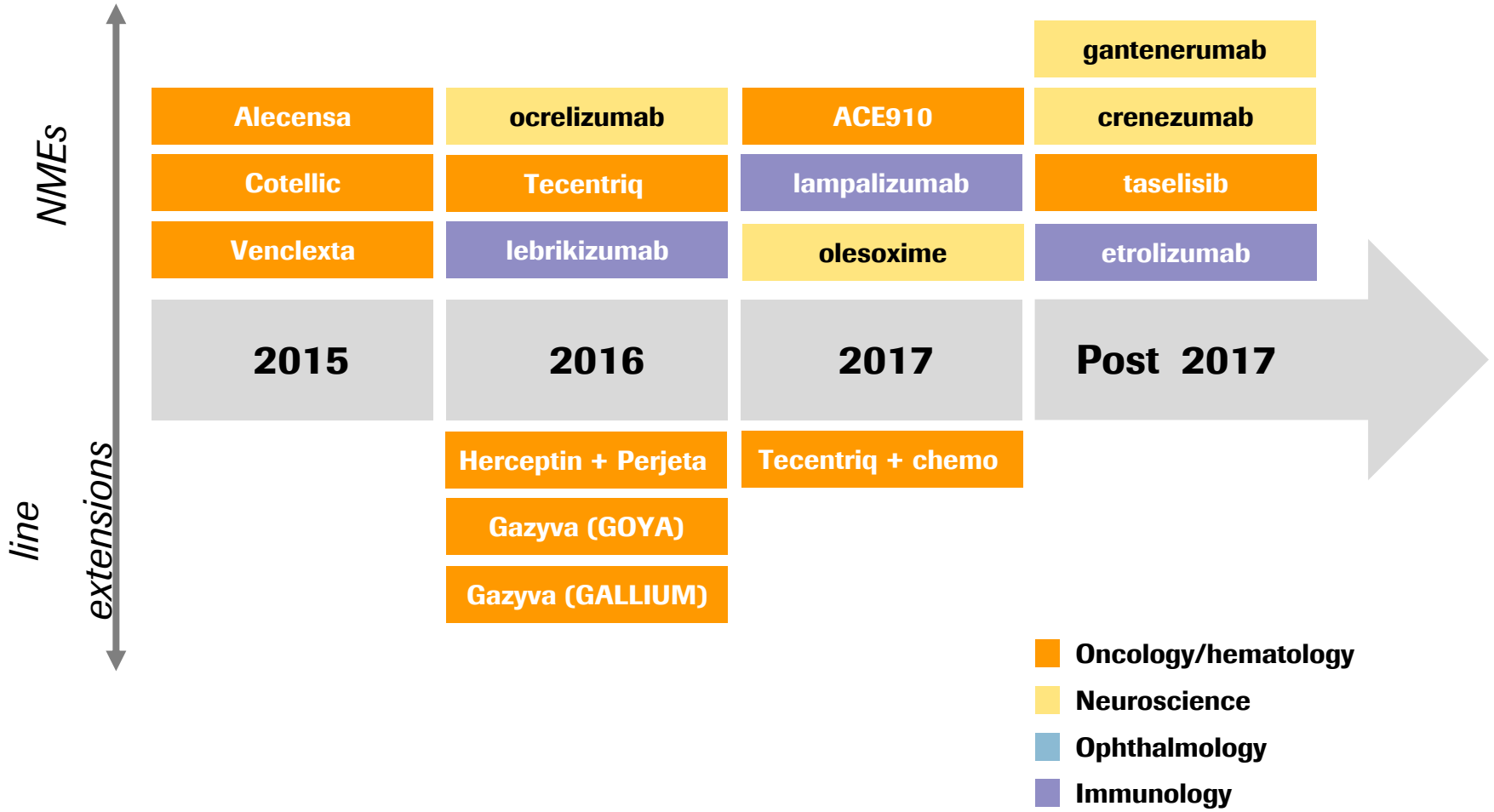
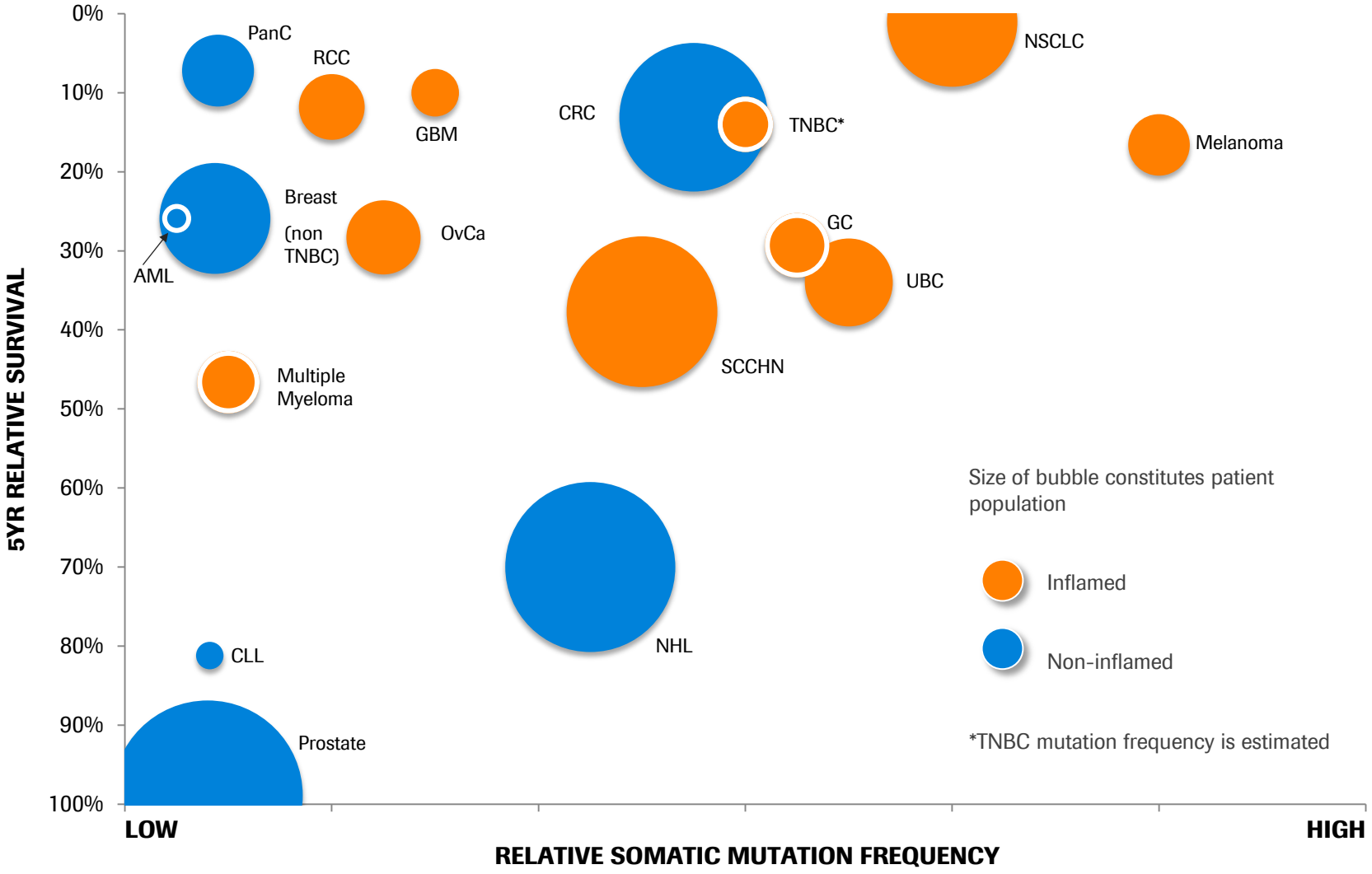


Roche: New growth opportunities

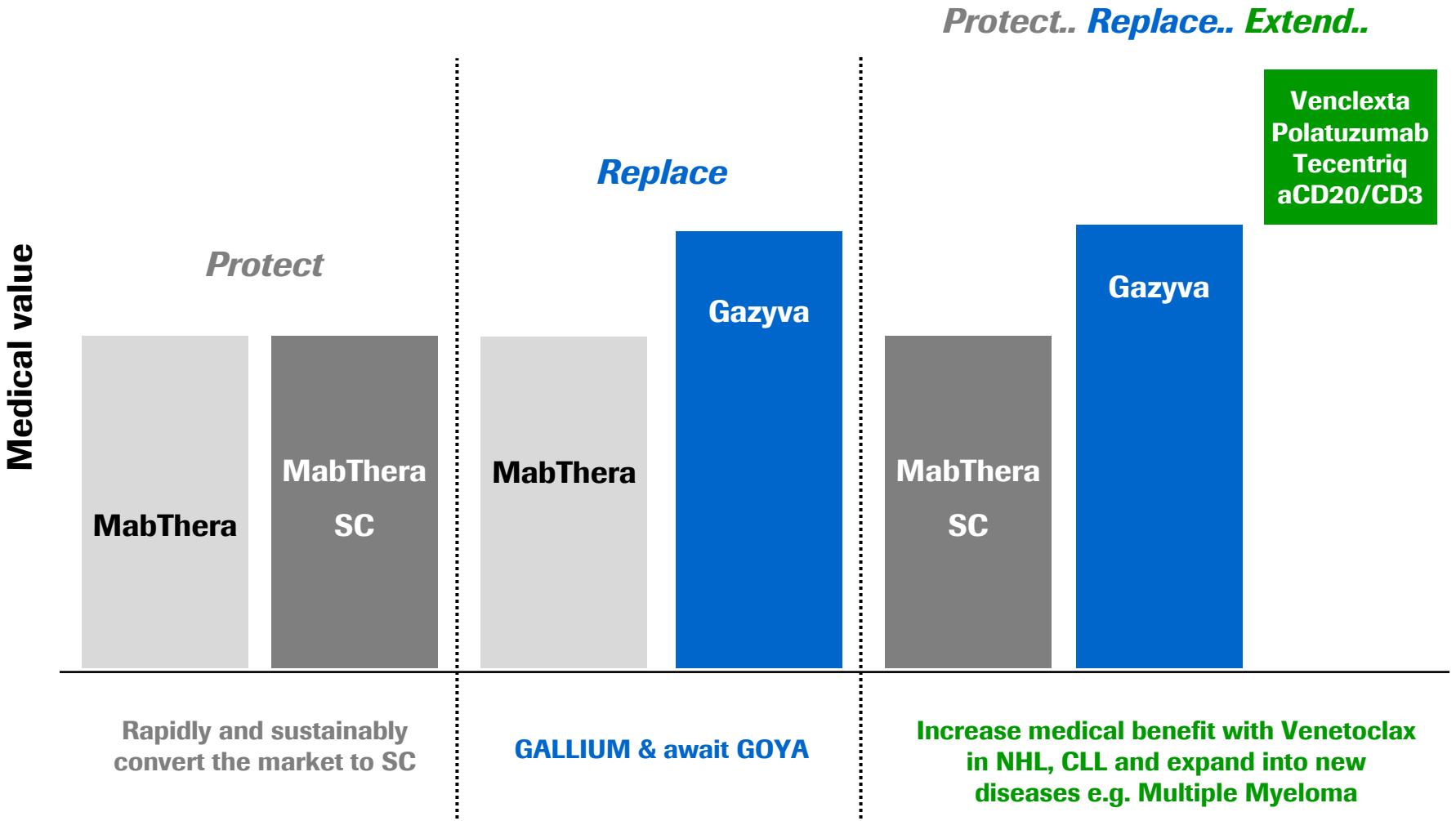


Investigating tumor specific strategies



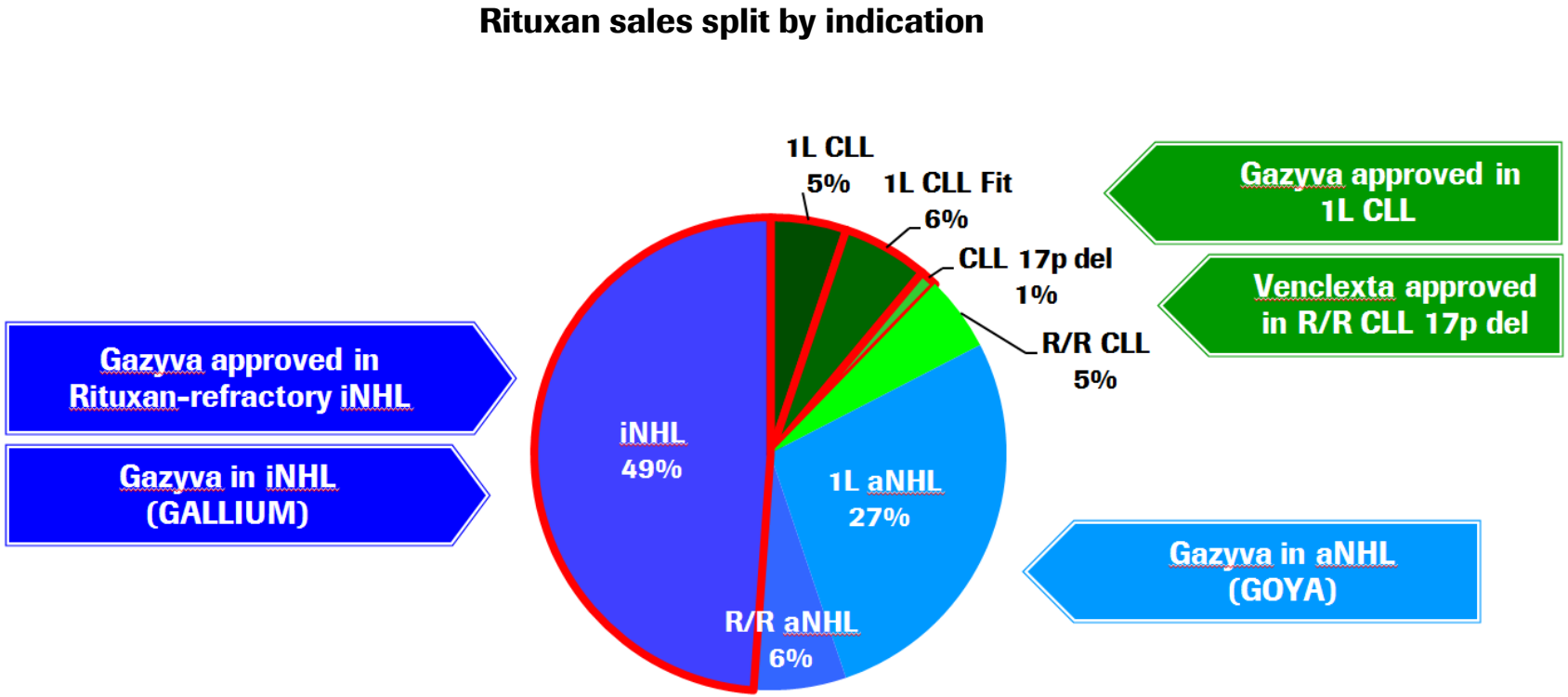
Strategies for long term growth

Anti-CD20 franchise



Venetoclax in collaboration with AbbVie; SC=subcutaneous; CLL=chronic lymphocytic leukemia; NHL=non-hodgkin's lymphoma

Establishing Gazyva as new CD20 backbone



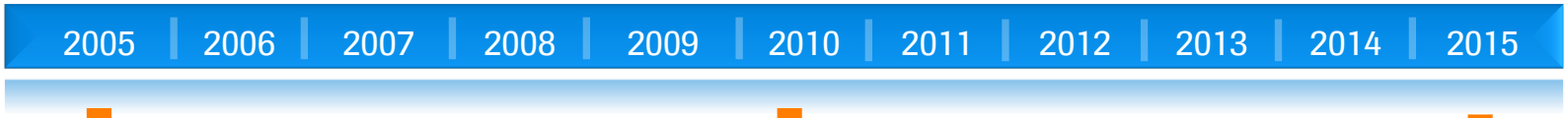
Pie chart shows 2014 Rituxan sales split according to indications; CLL=chronic lymphocytic leukemia; iNHL (FL)=indolent non-hodgkin's lymphoma; aNHL (DLBCL)=aggressive NHL; R/R=relapsed/refractory; Gazyva in collaboration with Biogen Idec

Biosimilars: Ten years in the making

Regulatory environment

Summary

Biosimilars: Ten years in the making



EU pioneered the BS concept

- Six products approved, including the first mAb BS (infliximab)
- Uptake did not achieve expected savings

WHO leading global efforts; many emerging countries implemented WHO BS Guidelines as a reference

Differential adoption of WHO BS guidelines led to registration of Non- Com-parable Biotherapeutic products (NCBs)*, driven by:

- Capacity issues at National Regulatory Agencies
- Local economic development policies

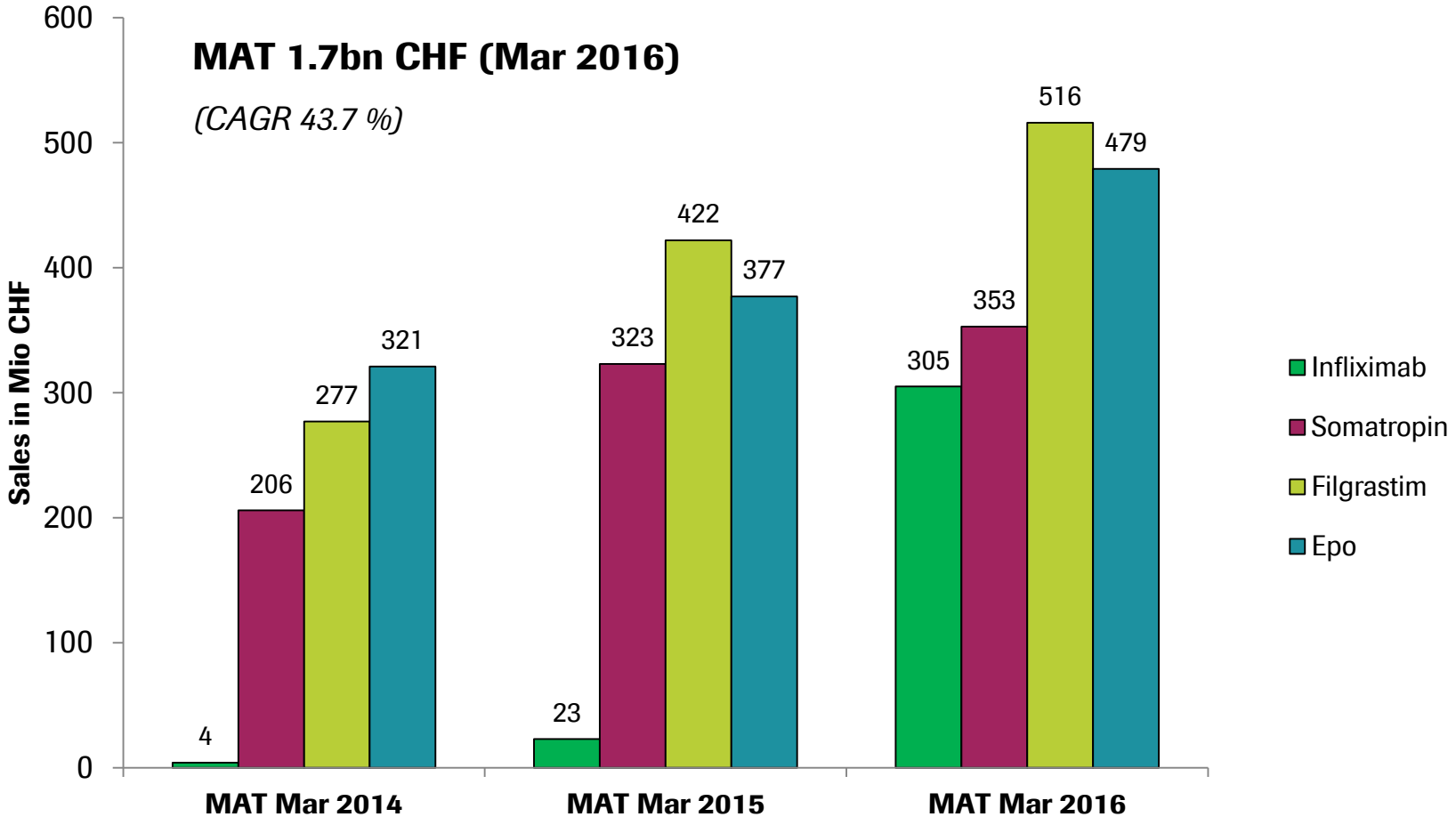
US published final BS guideline

- FDA pathway operating

BS entry timelines delayed (incl. Herceptin & MabThera)

*For definition and industry position on NCBs please refer to IFPMA Policy Statement:
http://www.ifpma.org/uploads/media/Non-comparable_Biotherapeutic_Products__English__01.pdfr

Current Biosimilar trends

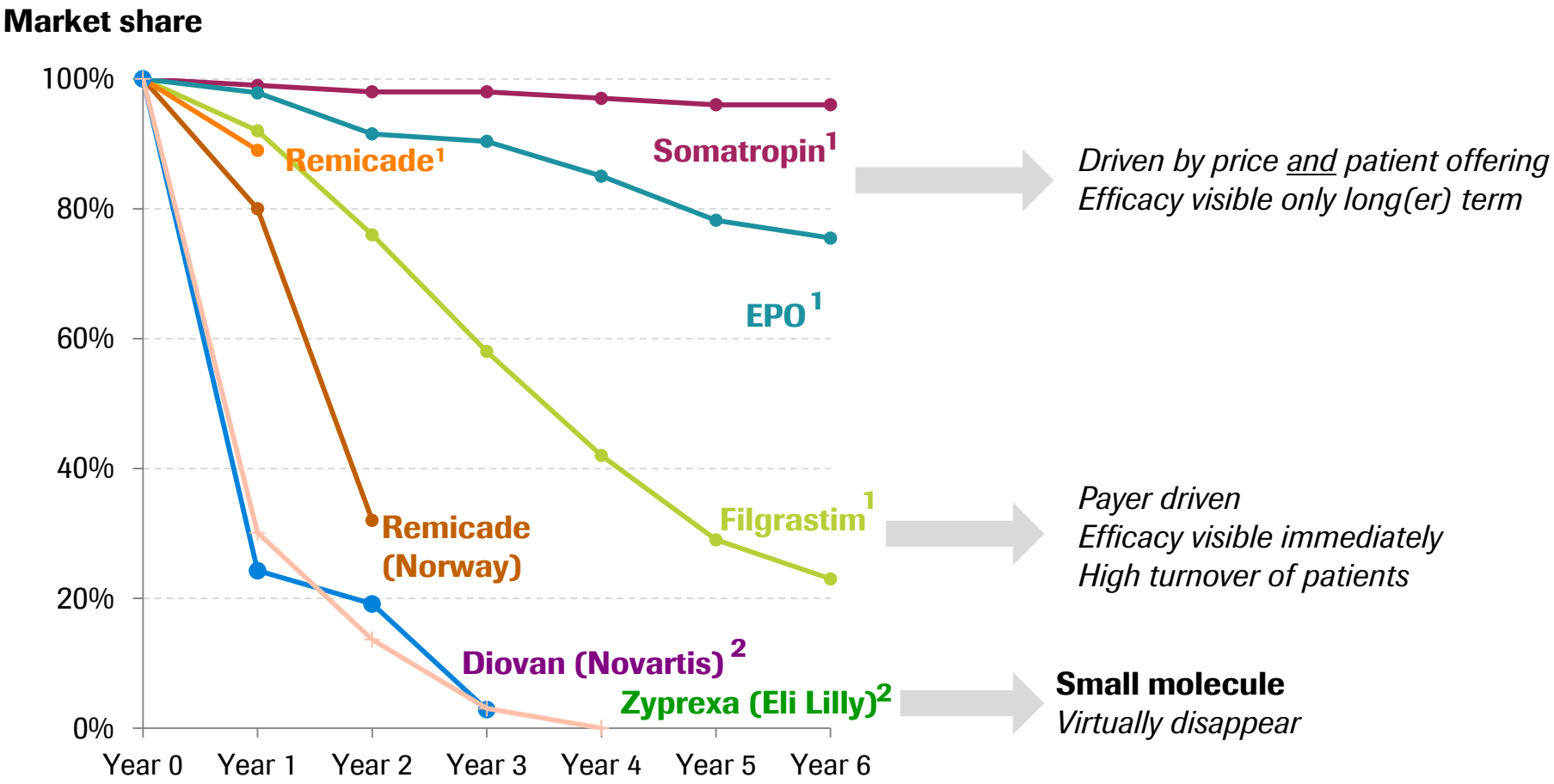


***Excludes pegylated Biosimilars**

Source: IMS Health. Based on Roche subscription of countries

Generics vs. Biosimilars

Clear divide in uptake; complex market drivers

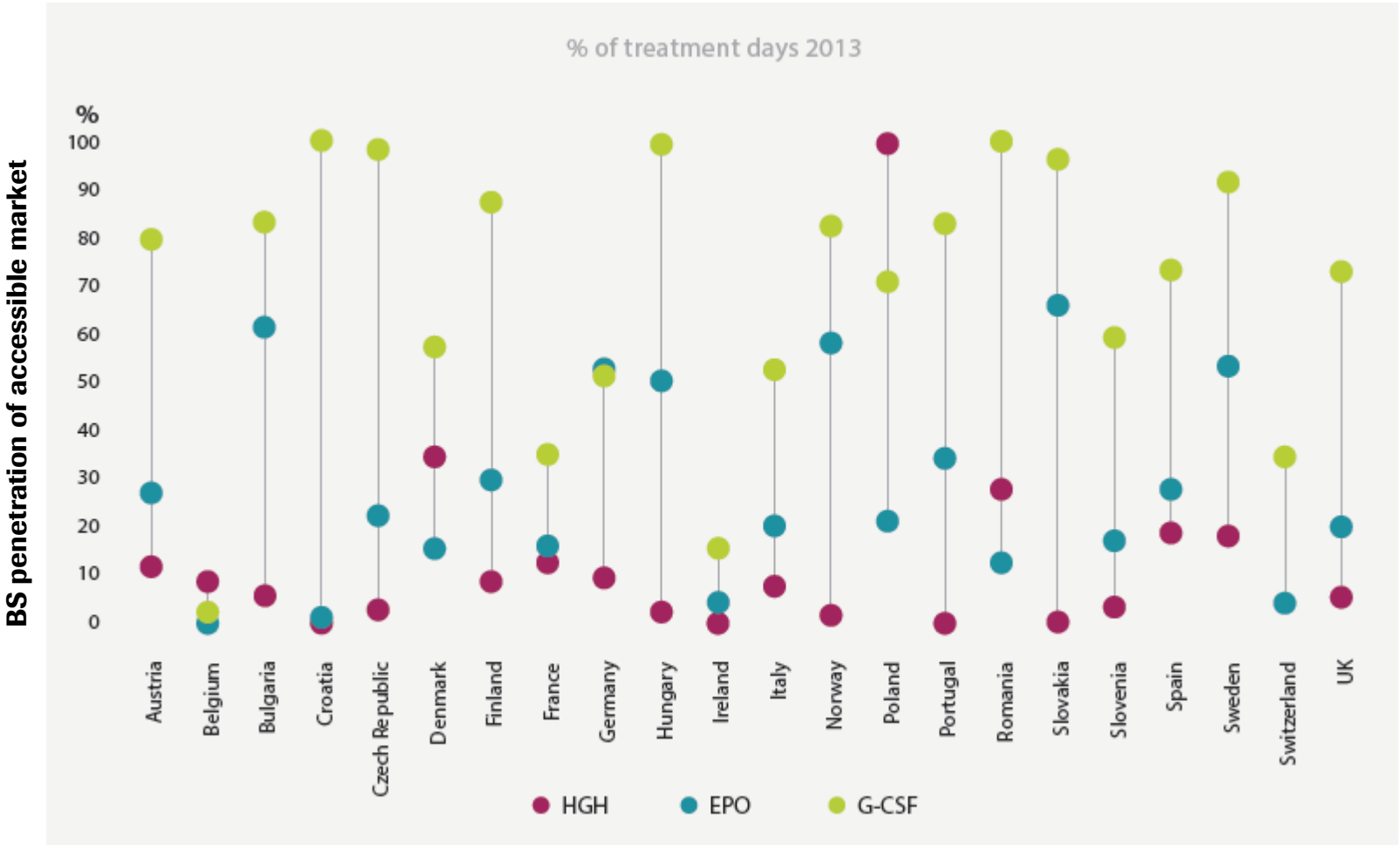


Sources: IMS Health, IMS & Roche analysis

[1] Volume market share based on EU5 average

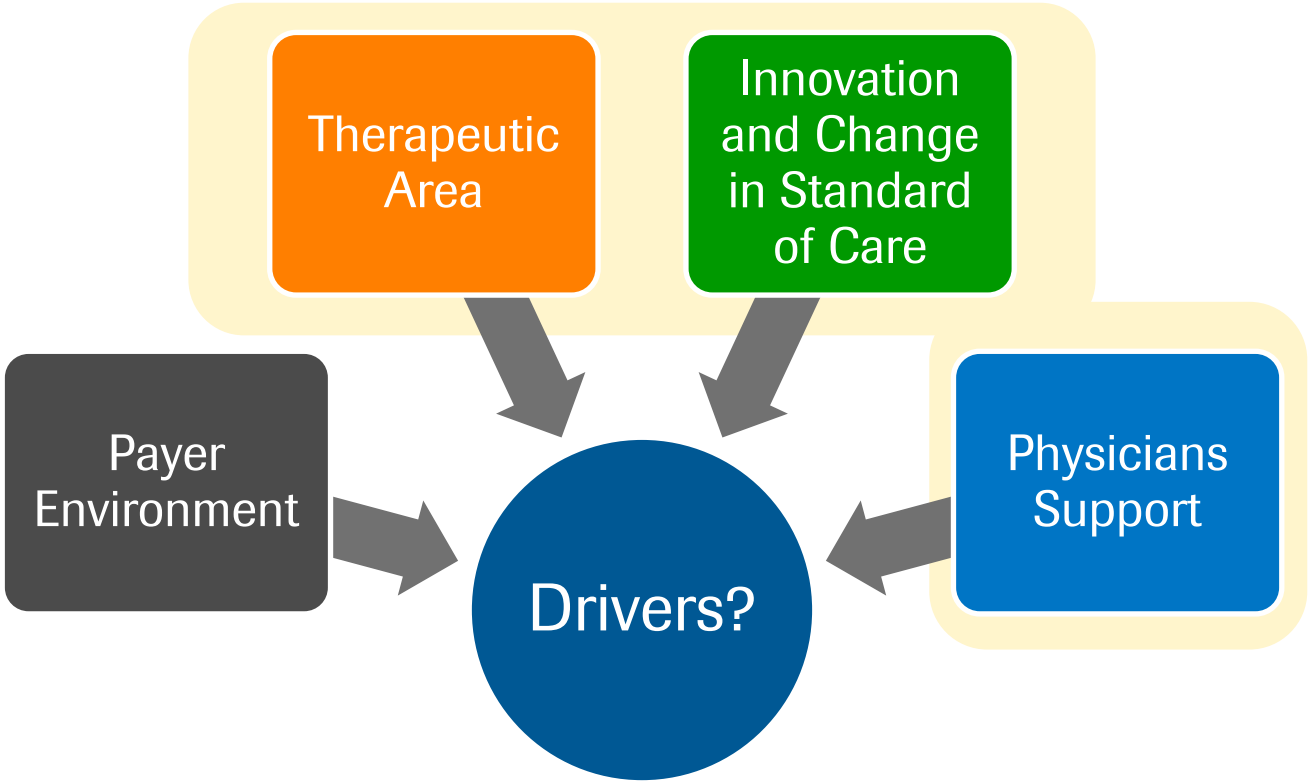
[2] Data based on % remaining sales in EU

Despite 10 years of experience in the EU, uptake of Biosimilars differ across countries



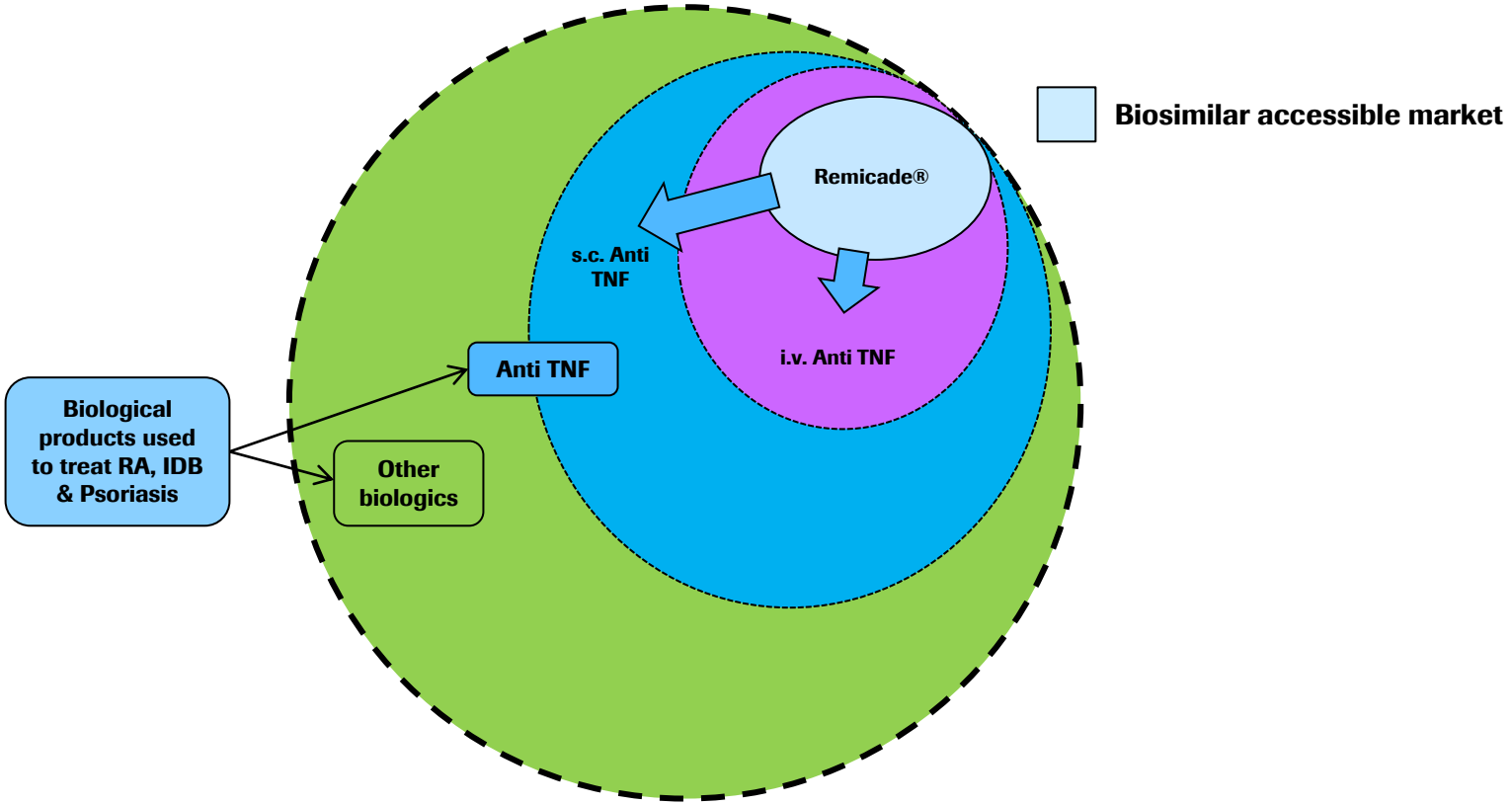
Reference: Assessing biosimilar uptake and competition in European markets. Report by the IMS Institute for Healthcare Informatics.

Payer environment is one of multiple drivers for Biosimilar uptake



Anti-TNF market is not a good analogue for oncology

Infliximab Biosimilar could expand beyond it's accessible market and obtain market share from Enbrel® and Humira®



Small molecules and biologics
Not all the same

- Small molecule policies allow substitution → only the price counts
- For biologics, European Medicine Agency (EMA) do not provide guidance on interchangeability and substitution
- Most countries in Europe have specific policies in place to distinguish between small molecule and biologic medicines
  - Biologics must be prescribed by brand name
  - Laws against substitution
  - Switching remains a physician decision

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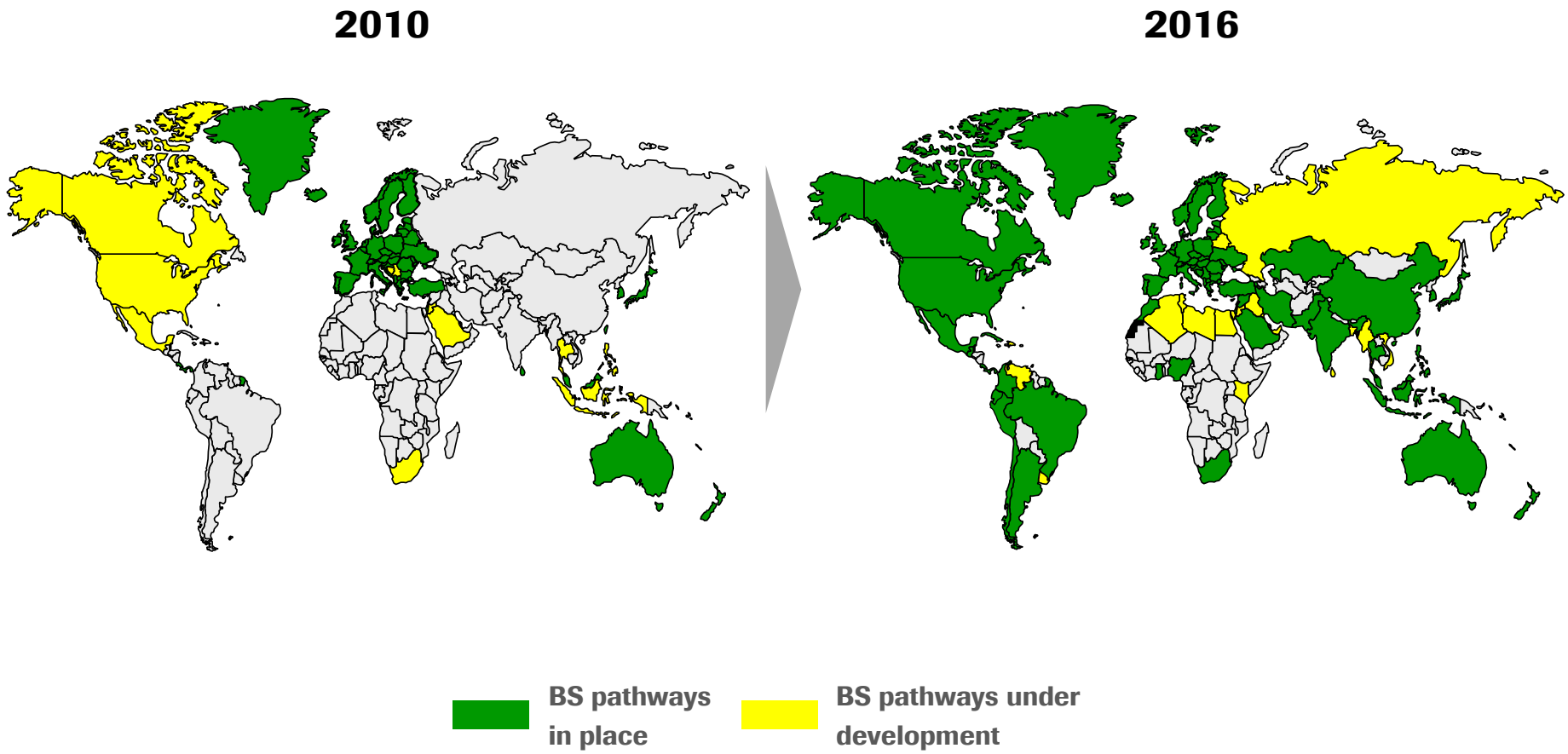
Establishment of Biosimilar guidelines has increased driven by WHO efforts



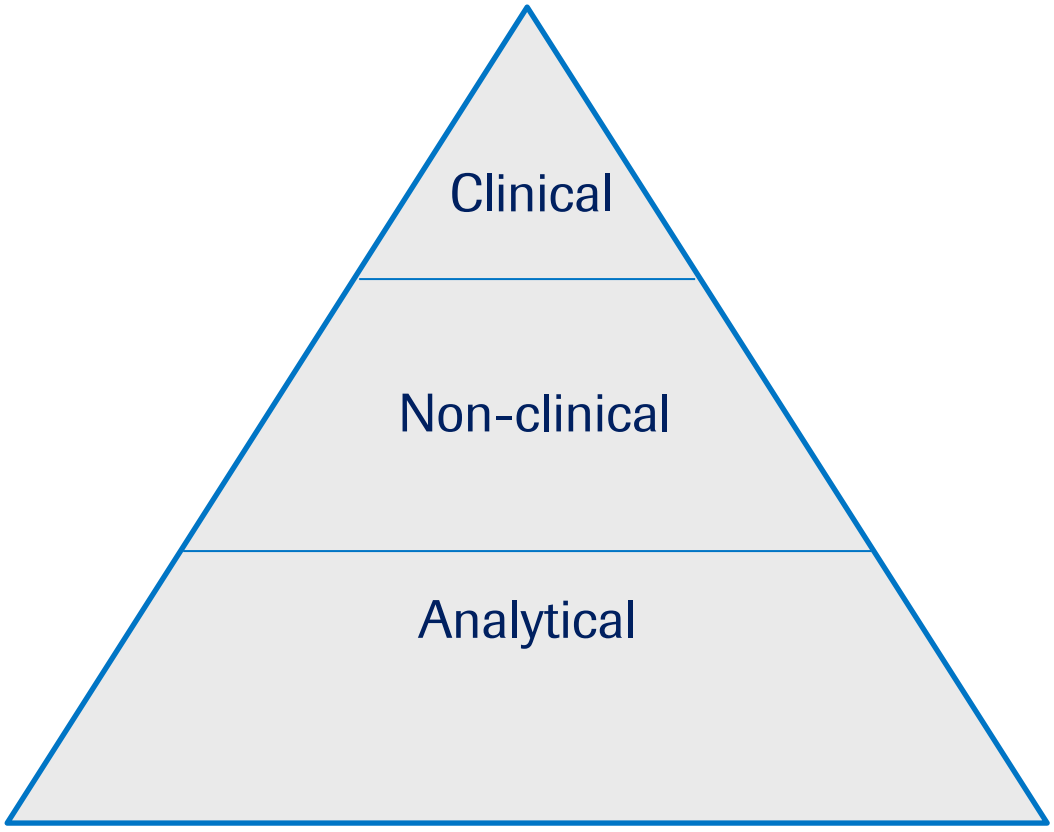
Requirements and study designs are different for the biosimilar vs. innovator

Aspects of development	Biosimilar	Innovator
Patient population	Sensitive and homogeneous (patients are *models*)	Any
Clinical design	Comparative versus innovator, normally equivalence	Superiority vs standard of care (SoC*)
Study endpoints	Sensitive, clinically validated PD markers	Clinical outcomes data or accepted/established surrogates (e.g. OS and PFS)
Safety	Similar safety profile to innovator; no new findings	Acceptable benefit/risk profile versus SoC*
Immunogenicity	Similar immunogenicity profile to innovator	Acceptable risk/benefit profile versus SoC*
Extrapolation	Possible if justified	Not allowed

* In some cases SoC may not exist

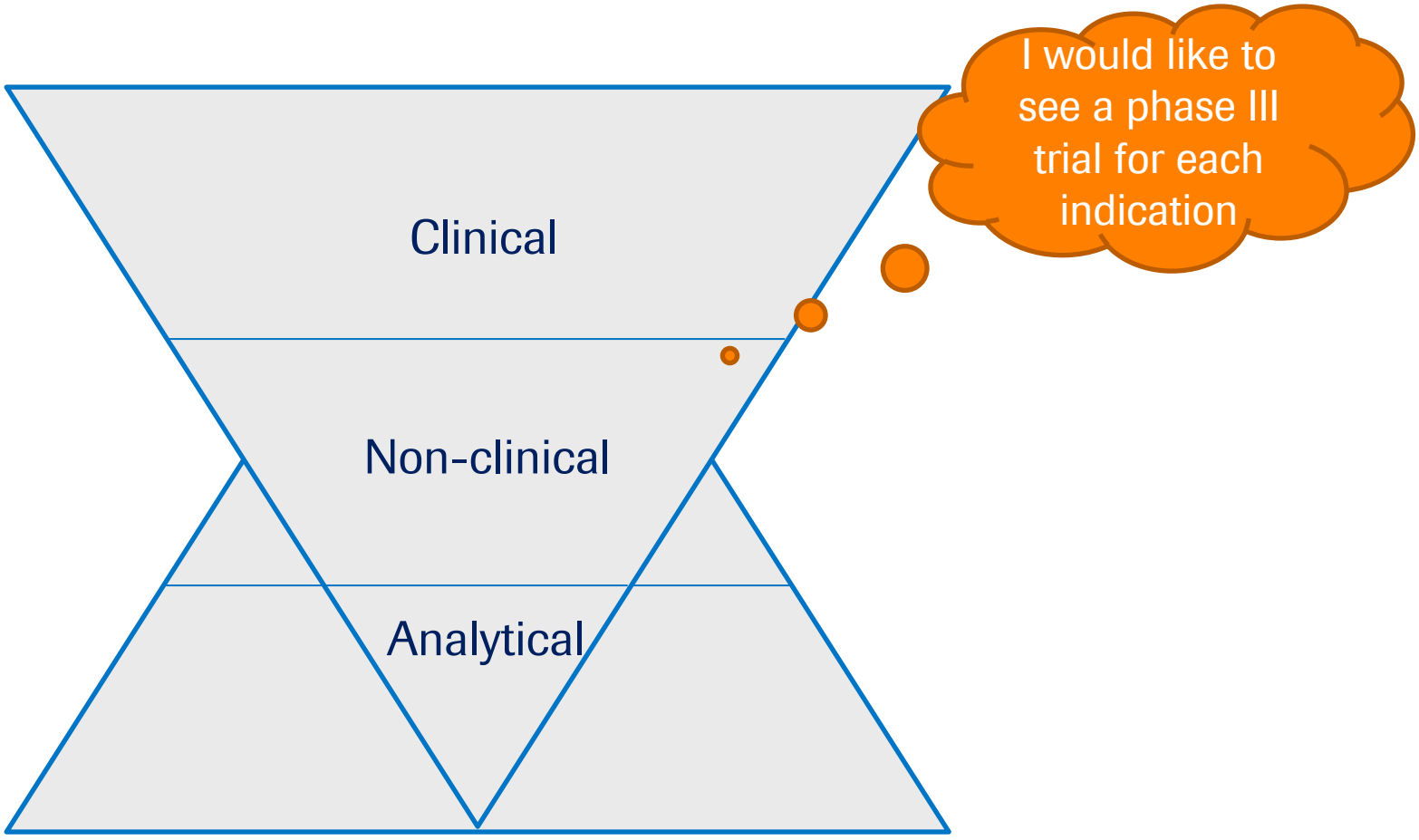
How should extrapolation risk be managed?

The regulator's perspective



How should extrapolation risk be managed?

The physicians' perspective

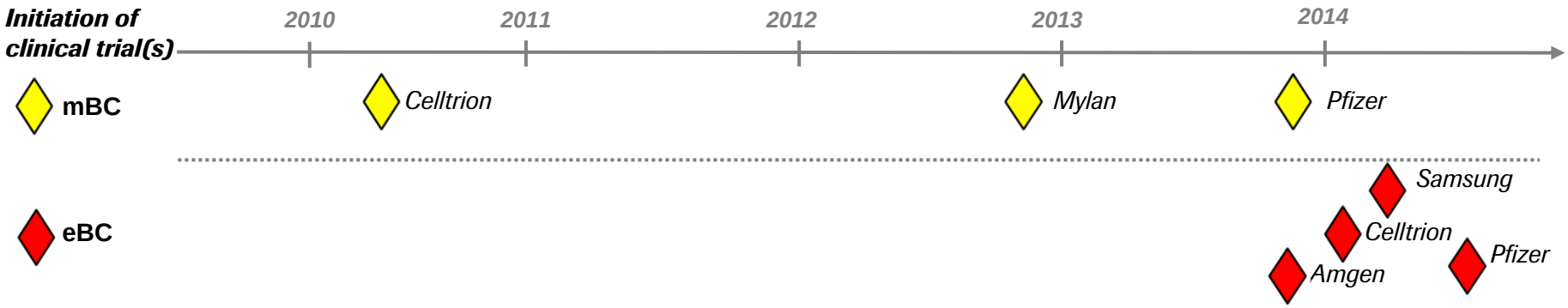


What is the right patient population to establish clinical similarity to Herceptin®?

Topic	Metastatic population (advanced)	Neoadjuvant/Adjuvant population (early)
PK	✘ Affected by patients status & tumor burden	✓ Homogeneous population can be selected
PD	✘ Clinically validated PD marker not available	
Clinical efficacy/safety	✘ • Difficult to select homogeneous group. • Need to control and stratify for multiple factors (e.g. prior use of chemotherapy, performance status…). • Population with heterogeneous characteristics affecting final clinical outcome.	✓ Populations less likely to be confounded by baseline characteristics and external factors
Immunogenicity	✘ Immune system affected by performance status and concomitant chemotherapies received	✓ Immune system impaired during chemotherapy cycles, but likely to recover to *normal* status thereafter

The regulatory thinking is evolving

The Herceptin® case



	mBC Phase III Start Date	Regulatory Filing	eBC Phase III Start Date
Celltrion	Q2 2010	✖	Q1 2014
Mylan	Q4 2012	?	
Pfizer	Q4 2013		Q2 2014
Samsung			Q2 2014
Amgen			Q4 2013

Biosimilar: 10 years in the making

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Generics, Biosimilars: Not all the same

- **Small molecules:** policies allow fast penetration of generics
- **Biosimilars:** countries in Europe have specific policies in place to distinguish between small molecule and biologic medicines:
  - Biologics must be prescribed by brand name, laws against automatic substitution, switching remains a physician decision, EMA - no guidance on interchangeability
  - After 10 years of experience in the EU, uptake of Biosimilars differ heavily across countries
- **Regulatory environment:** still evolving with authorities in the process of finally establishing frameworks; case by case decisions likely

Doing now what patients need next