Biologics & Biosimilars

Competition Law Challenges

David W. Hull

VAN BAEL & BELLIS

4 December 2018

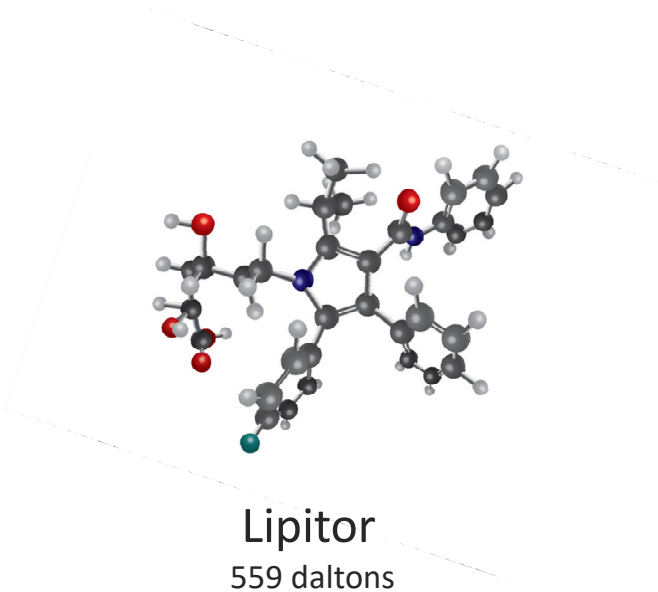
Biologics & Biosimilars

Biological Products

Biologics are medical products made from a natural source, for instance:

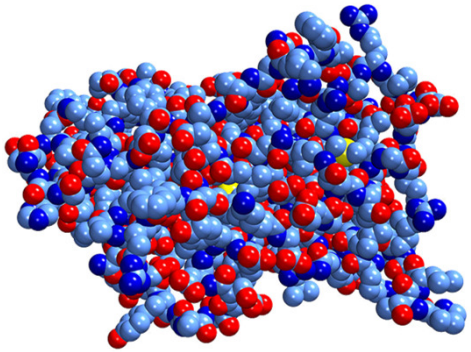
- Proteins, cells, allergenics
- Blood components or derivatives
- Viruses, vaccines, serums

Higher complexity products:



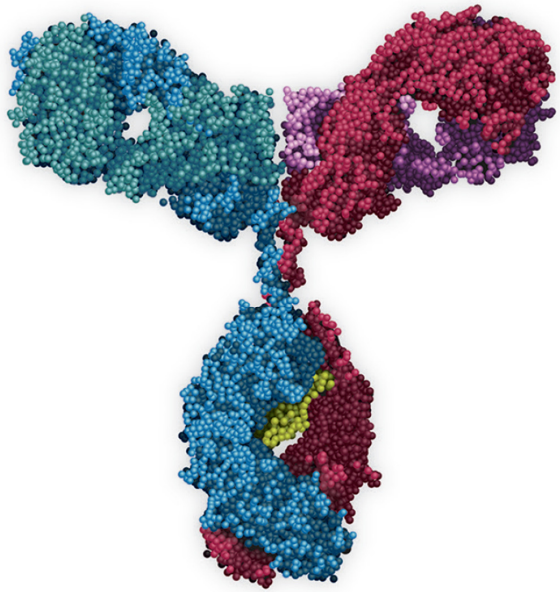
Lipitor
559 daltons

Small Molecule Drug



Human Growth Hormone
22,124 daltons

Small Biologic



Herceptin
185,000 daltons

Large Biologic

Source: Analysis Group

Biological Products

Biologics represent an increasing share of blockbuster drugs worldwide:

	2008	2009	2010	2011	2012	2013	2016
1	LIPITOR	LIPITOR	LIPITOR	SERETIDE	HUMIRA	HUMIRA	HUMIRA
2	SERETIDE	SERETIDE	SERETIDE	LIPITOR	SERETIDE	SERETIDE	HARVONI
3	PLAVIX	PLAVIX	HUMIRA	HUMIRA	HERCEPTIN	ENBREL	ENBREL
4	HERCEPTIN	ENBREL	ENBREL	ENBREL	ENBREL	HERCEPTIN	MABTHERA
5	ENBREL	HERCEPTIN	HERCEPTIN	HERCEPTIN	LIPITOR	MABTHERA	REMICADE
6	ZYPREXA	HUMIRA	LOVENOX	LOVENOX	MABTHERA	REMICADE	REVLIMID
7	LOVENOX	LOVENOX	AVASTIN	MABTHERA	LOVENOX	LOVENOX	AVASTIN
8	GLIVEC	GLIVEC	MABTHERA	AVASTIN	REMICADE	AVASTIN	HERCEPTIN
9	PANTOZOL	ZYPREXA	GLIVEC	REMICADE	AVASTIN	LUCENTIS	LANTUS
10	SYMBICORT	MABTHERA	ZYPREXA	GLIVEC	SPIRIVA	LYRICA	PREVNAR

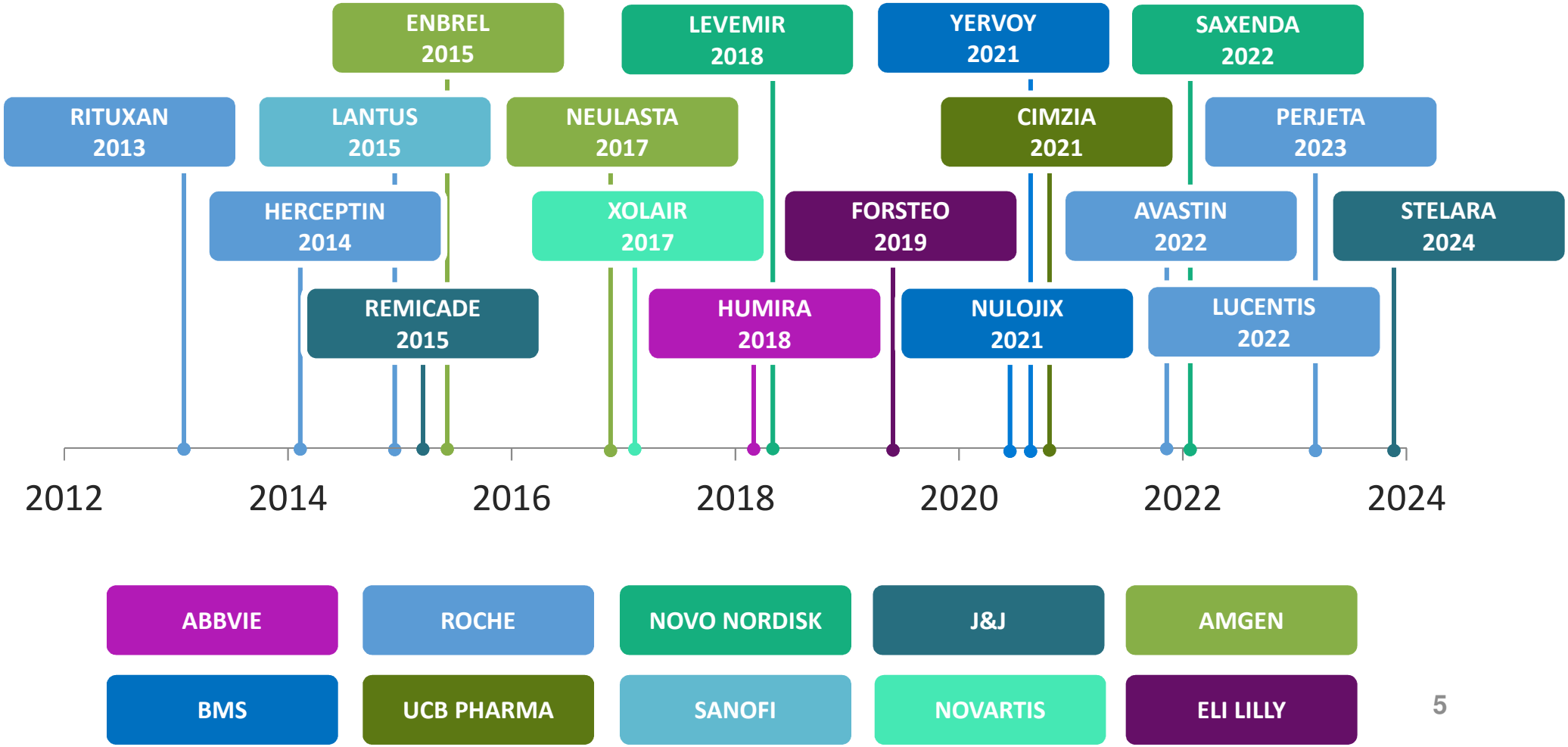
Source: International Bar Association

BIOLOGICS

SMALL MOLECULES

Biological Products

- Many blockbuster biologics have lost or will soon lose exclusivity soon



Biosimilars vs Generics

"A biosimilar is a biological medicinal product that contains **a version of the active substance** of an already authorised original biological medicinal product. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise needs to be established."

EMA Guideline on Similar Biological Medicinal Products

- A biosimilar is a biological medicine **highly similar** to another already approved biological medicine (the "reference medicine")
- Biosimilars are approved according to the **same standards** of pharmaceutical quality, safety and efficacy that apply to all biological medicines:
  - Comprehensive comparability studies and solid pharmaceutical quality data
  - Biosimilar can rely on efficacy and safety experience of reference product
  - Extrapolation of other indications is possible if scientific evidence addresses all specific aspects of these indications
- A biosimilar is not regarded as a generic of a biological medicine, primarily because the natural variability and more complex manufacturing of biological medicines do not allow an exact replication at the molecular level

Biosimilars vs. Generics

Generics	Biosimilars
Small molecule	Large, complex molecule
Simple manufacturing process: • Structure can be readily recreated from examining reference product • Process can be changed substantially while preserving end result	**Complex manufacturing process:** • Manufacturing process is integral to success of end product • Minor changes in production can dramatically alter function
Straightforward development: • Limited scientific know-how required • Limited clinical tests • High success rate	**Complex development:** • Extensive R&D required • More extensive clinical trials required • Lower success rate
Low cost to bring to market (€2-3 million)	**High cost to bring to market** (€100-200 million)

Biosimilar Entry

Like generics, biosimilar entry has a pro-competitive effect that generally results in benefits for payors, national health budgets and patients

Generate Savings

Biologic entry leads to price erosion

Improve Access

Creates alternative supply, more options

Incentivize R&D

Encourages R&D into new “biobetters”

But, because biosimilars are not generics:

- They face higher entry barriers (both cost and time)
- Manufacturers will require a significant ROI to enter the market
- Therefore a minor reduction in a biosimilars’ ability to penetrate the market and recoup costs will have major effects on the attractiveness of these markets to future entrants

Strategies to Delay Biosimilar Entry and Uptake

Originator Strategies to Delay Biosimilar Entry

In the context of generic entry, the Court of Justice has already made clear that late lifecycle strategies are allowable, provided they represent competition on the merits:

> *"[…] the preparation by an undertaking, even in a dominant position, of a strategy whose object it is to minimise the erosion of its sales and to enable it to deal with competition from generic products is legitimate and is part of the normal competitive process, provided that the conduct envisaged does not depart from practices coming within the scope of competition on the merits, which is such as to benefit consumers."*
>
> Case C-457/10, *Astra Zeneca*

Originators of biological products have the same incentives as small molecule originators to delay the entry of new competitors:

- Price erosion occurs quickly once a biosimilar enters the market, so any delay will have a substantial effect on profit margins

Originator Strategies to Delay Biosimilar Entry

Delaying biosimilar entry may be easier than delaying generic entry:

- Fewer companies have the sophistication to produce biosimilars, so there may be one or very few competitors entering the market at the time of patent expiry

- Biosimilars are not identical to their reference product, and their authorization is more complex, which presents more opportunities to interfere with their entry on the market

- Biosimilars are newer products, and therefore HCPs may be less familiar and more risk averse with respect to their use, which provides opportunities to discourage HCPs from switching from the reference product

LESS LIKELY

- Reverse patent settlements
- "Product hopping"

MORE LIKELY

- IP/Regulatory Abuse
- Product denigration

Abuse of the IP and Regulatory System

In the context of generics, competition authorities have already found that it is abusive to:

- Make false or misleading representations during regulatory/IP process
- Intervene in the authorization process of a generic without a good-faith basis to hinder generic entry

Astra-Zeneca (2000)

- When registering its SPC for Losec in national patent offices, AstraZeneca listed the date Losec first entered the EU market rather than the date it was granted an MA

AstraZeneca used the later date knowing the regulatory authorities would assume the date referred to its MA approval rather than its market entry, and did not explain that it was using a different date

- By intentionally misleading patent authorities AstraZeneca obtained longer patent protection for Losec against generic entrants
- **European Commission fine: €60 million**

Abuse of the IP and Regulatory System

Janssen-Cilag (2017)

- Ratiopharm's generic fentanyl patch had received approval through a centralized process following a lengthy EMA investigation
- Although the French authority was required to approve the generic, Janssen made numerous interventions citing safety concerns

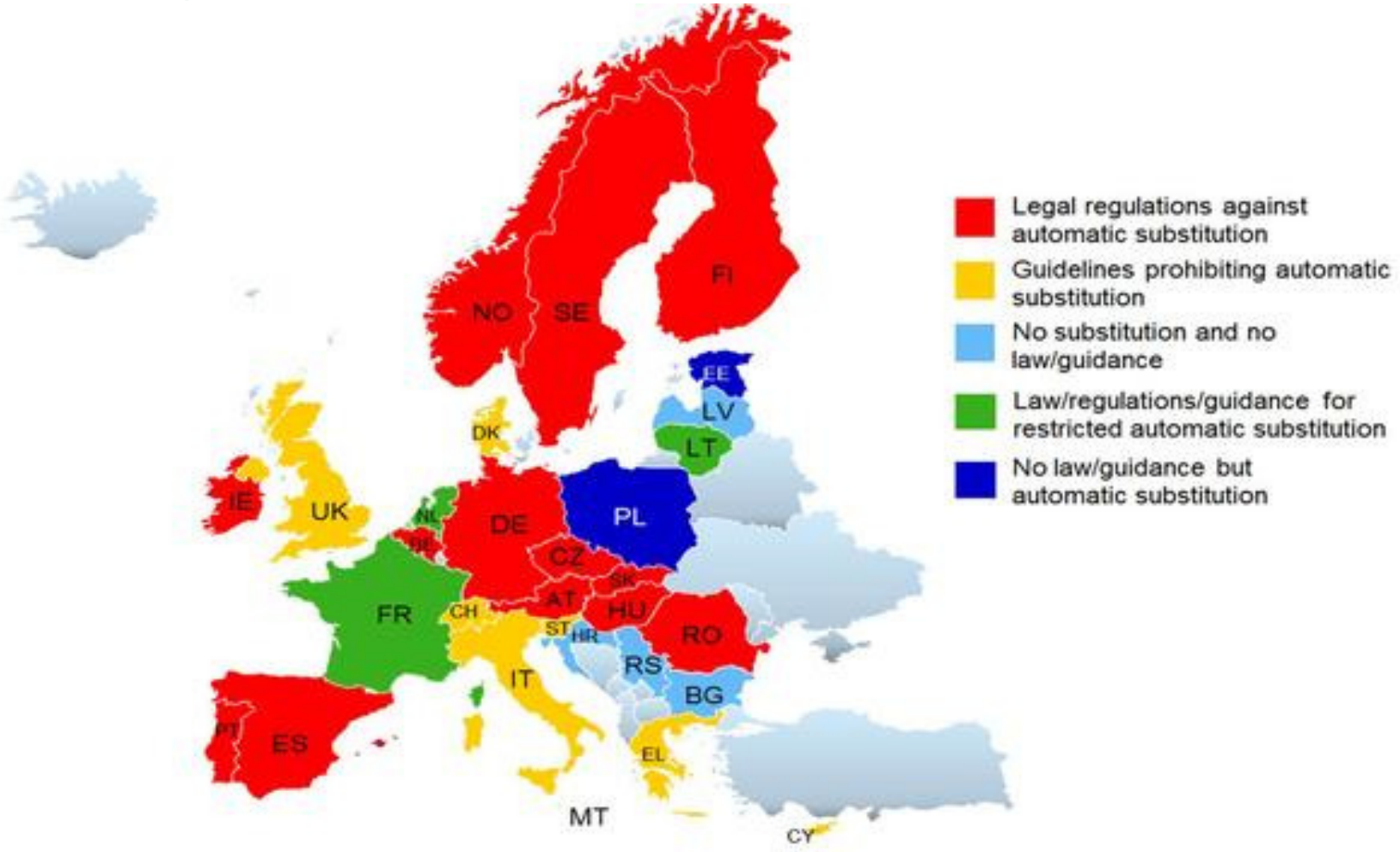
Janssen-Cilag raised its safety concerns regarding differences between the generic (dosage, patch size) even though these issues had already been addressed at the European level

- By intervening in the French MA process and circumventing the European framework, Janssen-Cilag was able to delay recognition of Ratiopharm's generic by a year
- **European Commission fine: €25 million**

Abuse of the IP and Regulatory System

Biosimilars face a higher risk of such kinds of regulatory abuse:

- Questions of IP, market authorizations for biosimilars are highly complex
- While the MA process is centralized, automatic substitutability is left to the national level



Abuse of the IP and Regulatory System

The issue of whether a biosimilar may be used for additional indications is not as straightforward as with generics

- Requires a complex assessment (**extrapolation)**

> *"If biosimilarity has been demonstrated in one indication, extrapolation to the other indications of the reference product **could be acceptable with appropriate scientific justification**."*
>
> EMA Guidelines on similar biological medical products

- This involves a multifaceted analysis:

Bottom line: there are so many factors involved that a an originator company could easily raise doubts at national or EU level to delay the entry of generics

Abuse of the IP and Regulatory System
EXAMPLES

Originator biologic takes improper steps to extend its market exclusivity, for example by:

- Registering for additional patents solely for the purpose of blocking entry
- Supplying misleading information to the EMA regarding the scope of its patent or RDP rights

Originator biologic takes improper steps to delay biosimilar entry by interfering in national procedure, for example by raising unfounded:

- IP concerns in procedures to allow market access of biosimilars
- Safety concerns in procedures to determine interchangeability, switching and substitution between the biosimilar and its reference product

Product Denigration

Competition authorities have found it is abusive to make false or misleading statements:

- Suggesting without evidence that there is a problem with the safety or efficacy of generics
- Mentioning irrelevant differences between generics and reference products

Sanofi-Aventis (2017)

- Generics for Sanofi's Plavix used a different salt (because Sanofi had a patent on the salt) and had one more indication than generics

Sanofi told doctors about the different salt without explaining that it was clinically irrelevant. It also held out Plavix as having been time-tested while characterizing generics as untested and therefore dangerous

- Although **true**, Sanofi's statements were **misleading**
  - They implied the generic was inferior without any medical basis
  - This might make doctors less likely to prescribe the generic
- **French competition authority fine: €40.6 million**

Product Denigration

The French Competition Authority noted that certain characteristics of the pharmaceutical market heightened the anticompetitive effects of misleading statements about **generics**:

- HCPs are slow to take up a new product without fully understanding it
- HCPs are extremely risk averse with respect to product safety
- HCPs do not usually understand the approval process or pharmacology and will therefore accept statements about product characteristics at face value

These factors will be even further pronounced in the case of **biosimilars**:

- HCPs cannot determine autonomously whether a biosimilar is really functionally equivalent in all relevant respects to its reference product, and will rely on the MA and representations from pharma companies
- There are by definition differences between a biosimilar and a reference product, so there may be some leeway for the originating company to mention these distinctions because they may not be irrelevant in all circumstances
- There is also considerable margin to mislead on off-label use and extrapolation, as this is a subjective assessment of many factors

Product Denigration
EXAMPLES

Originator biologic makes false or misleading claims about competing biosimilars such as:

"Our product has been the **tried and true** treatment for this condition for 10 years."

"The biosimilar is **scientifically different** from our original product."

"We have **clinical studies** for the use of our product for this indication, the biosimilar is only authorized to treat it by **extrapolation**."

"Do you want to take the risk of using a biosimilar to treat this **serious condition**?"

"While the biosimilar has been authorized at the European level for now, there are **many doubts** about whether they are violating our patents."

Reverse Payment Patent Settlements & Product Hopping

While possible, reverse payment patent settlements and product hopping are unlikely to be the most common forms of abusive action taken by originator companies against biosimilars

Reverse Payment Patent Settlements

- Certain transfers of payments to generics in exchange for their agreement to delay market violate competition law
- Biosimilar companies invest many hundreds of millions of euros to bring a biosimilar close to gaining a market authorization
- It is less likely that biosimilars would have the financial incentives to accept a pay-for-delay settlement

Product Hopping

- Forcing a switch from treatments that are going generic to next-generation regimens that confer little clinical value may violate competition law
- Biologics are complex, and minor tweaks in manufacturing methods (e.g. from capsule to tablet) can have major impact on effectiveness
- Research more likely to focus on development of “biobetters” with real clinical benefit