

Biosimilars Substitution Impact

Market Insights

*Situation Analysis
&
Strategic Options*

The purpose of this project is to help pharma companies define an optimal strategy considering the expected extension of biosimilars authorized to be substituted by retail pharmacists

Introduction

Context

- The art. 54 of LFFS 2024 published in December 2023 authorizes the substitution by retail pharmacists of biosimilars, two years after market entry, unless the ANSM gives a negative opinion
- This change in the retail market environment should have different impacts on the companies marketing biosimilars according to their product portfolio and their current presence at retail pharmacy level

Objective

- The objective of this study is to evaluate:
 - The likely changes re. the substitution of biosimilars over the 2024 – 2027 period, on the retail market
 - The possible impacts on the behavior of involved stakeholders
 - The specific strategic implications for pharma companies depending on their competitive position and ambition

Methodology

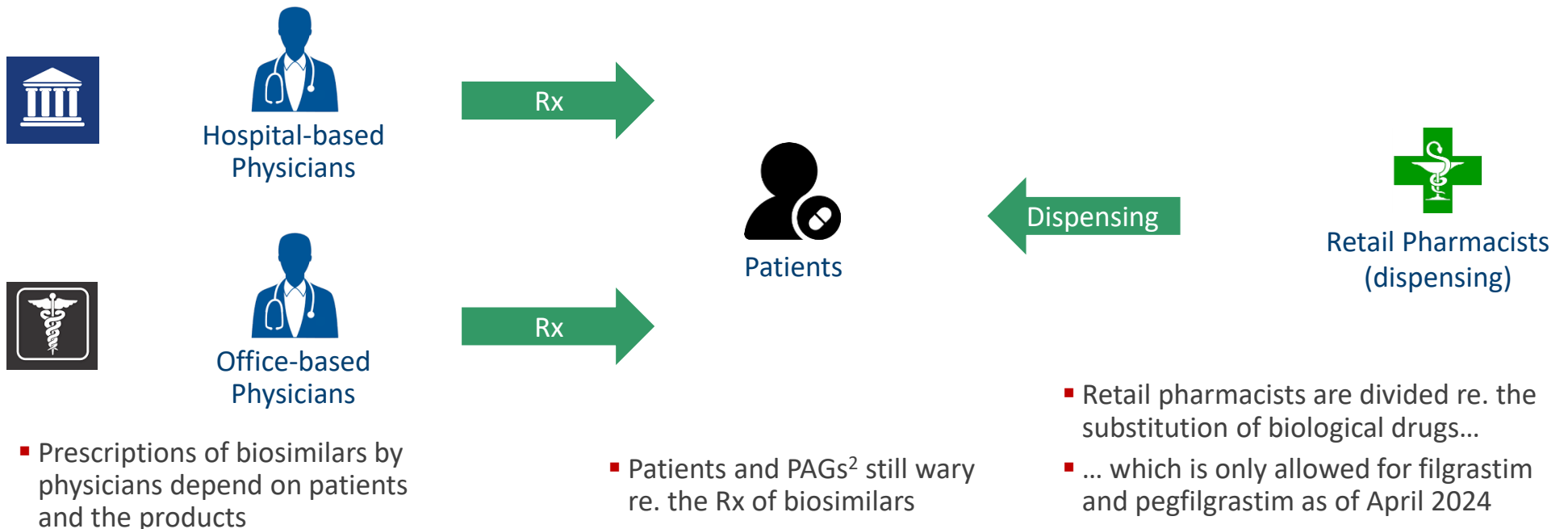
- Desk research re. the implementation of the law re. biosimilars substitution, stakeholders' opinion and behaviors
- Interviews of key stakeholders to gather information re. their vision, opinion and likely behavior:
 - Professional associations: Leem – Gemme – FSPF – USPO – Federgy – CNGPO
 - 9 Pharma companies operating on the retail biosimilars market
- Market scenario building and strategic option development and evaluation for pharma companies operating on the retail biosimilar market

So far, the development of the biosimilars retail market has been mostly driven by the prescription of hospital and office-based physicians which is encouraged by health authorities

Stakeholders involved in the French biosimilars market

Health Authorities & Payers¹

- Health authorities and payers have introduced a series of measures to convince hospital and office-based physicians to prescribe more biosimilars, either as an initial treatment or as a switch



The French retail biosimilars market requires from pharma companies, strategies, tactics and organizational models to succeed that are different from the hospital market segment ones

Specificities of the retail biosimilars market

Definition

- Prescribed by hospital and/or office-based specialists, purchased and delivered by retail pharmacies only (e.g., follitropin alfa, somatropin) or by hospital pharmacies too (e.g., epoetin, filgrastim)

Pricing

- Ex-factory price initially set by the CEPS at -40% below the price of the original biologic before its price is cut, following biosimilars entry

Purchasing

- The level of rebates to retail pharmacies is legally limited to a maximum of 2.5% of the ex-factory price which is in general granted by wholesalers¹
- Limited price pressure on retail sales

Medico marketing activities

- Medical activity carried out by MSLs to reassure prescribers about the quality of the biosimilars
- Promotional activity carried out by marketers and med reps to be prescribed to in- and out-patients

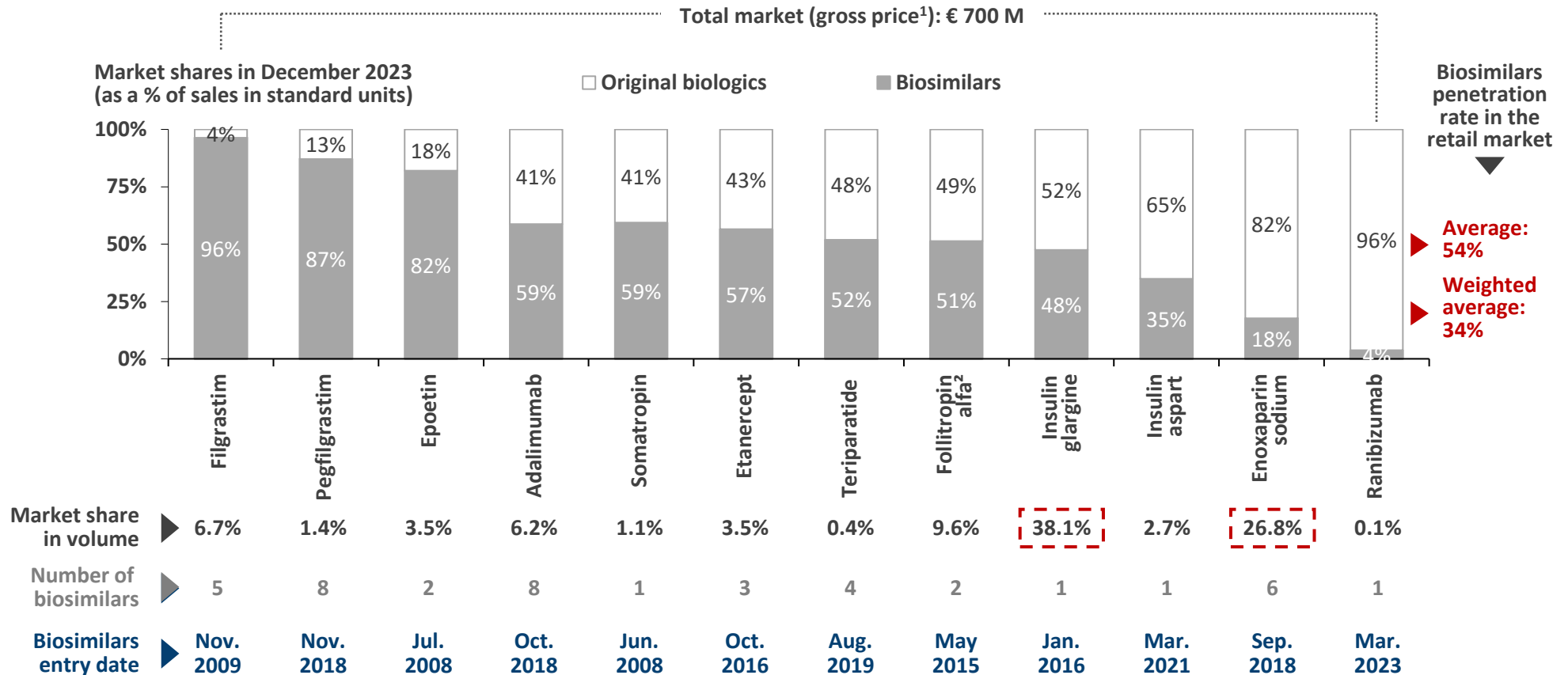
Substitution of biosimilars by retail pharmacists is yet allowed for filgrastim and pegfilgrastim, and should be extended to additional biologics, from 2024 onwards

Regulations related to biosimilars

Biosimilar drugs¹	Inter-changeability	<ul style="list-style-type: none"> The ANSM has specified in May 2016 that inter-changeability was possible between biologic drugs belonging to the same similar biologic group
	Biosimilar register	<ul style="list-style-type: none"> The ANSM² has created in 2017 similar biologic groups, each of them defined by an original biologic and its corresponding biosimilars, listed by brand name
<ul style="list-style-type: none"> A biosimilar drug is any biological drug that has the same qualitative and quantitative composition of active substance and the same pharmaceutical form as an original biologic... ... but does not fulfill the conditions for being regarded as a generic due to differences related to raw material variability or manufacturing processes requiring the achievement of additional preclinical and clinical data under regulatory conditions... ... demonstrating that the biosimilar: <ul style="list-style-type: none"> Is similar to the original biologic Does not differ significantly from the originator in terms of quality, efficacy and safety 	Biosimilar substitution right	<ul style="list-style-type: none"> France allowed the substitution of biosimilars, in December 2013, but in the absence of implementation decrees, this law has never been implemented After having been abrogated in 2020, the substitution right has been reintroduced in 2022, with a decree authorizing the substitution by retail pharmacists of 2 products: filgrastim and pegfilgrastim The Article 54 of the PLFSS 2024 stipulates that two years after the publication of the reimbursement listing of the first biosimilar, in a given group, a decree will authorize the substitution by retail pharmacists within this group, unless the ANSM issues an opinion to the contrary before the end of these two years Substitution is possible, provided: <ul style="list-style-type: none"> The biological products belong to the same similar biologic group The prescriber has not explicitly prohibited, in writing, the substitution of the prescribed drug The retail pharmacist has informed the prescriber, the patient and recorded the details of the biosimilar delivered The biological product delivered does not induce higher costs³

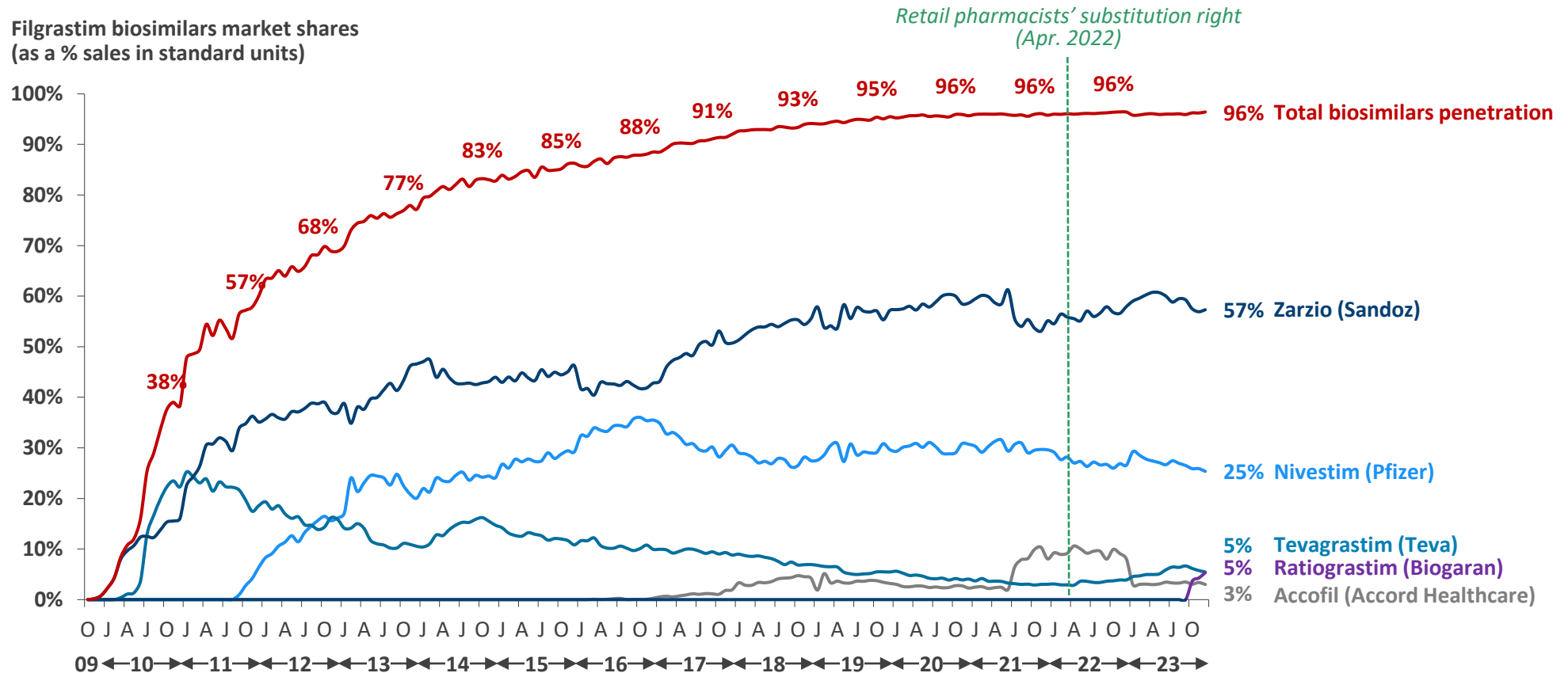
In December 2023, the weighted average retail biosimilars penetration rate was limited to ~34%, pulled down by insulin glargine and enoxaparin sodium which accounted for ~65% of the volumes

Retail biosimilars penetration rate (2023)



Retail pharmacists' substitution right had no significant impact on both biosimilar penetration (which already reached ~96% before the authorization) and market shares amongst biosimilars

Filgrastim biosimilars penetration in volume (retail market)

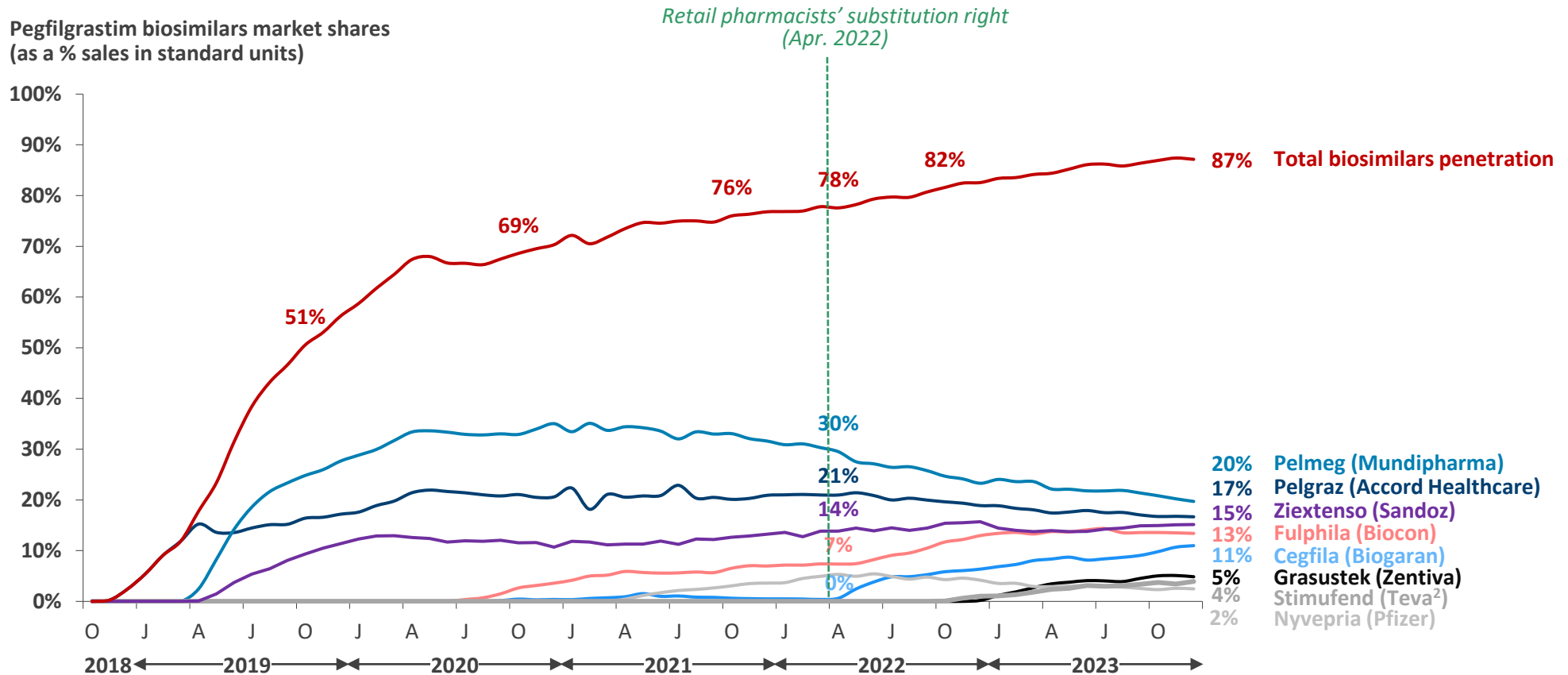


Sources: ANSM – GERS (December 2023) – Smart Pharma Consulting analyses

Retail pharmacists' substitution right led to a strong uptake of Biogaran (+11 pts MS) and Biocon¹ (+6 pts MS) to the detriment of Mundipharma (-10 pts MS) and Accord Healthcare (-4 pts MS)

Pegfilgrastim biosimilars penetration in volume (retail market)

Pegfilgrastim biosimilars market shares
(as a % sales in standard units)

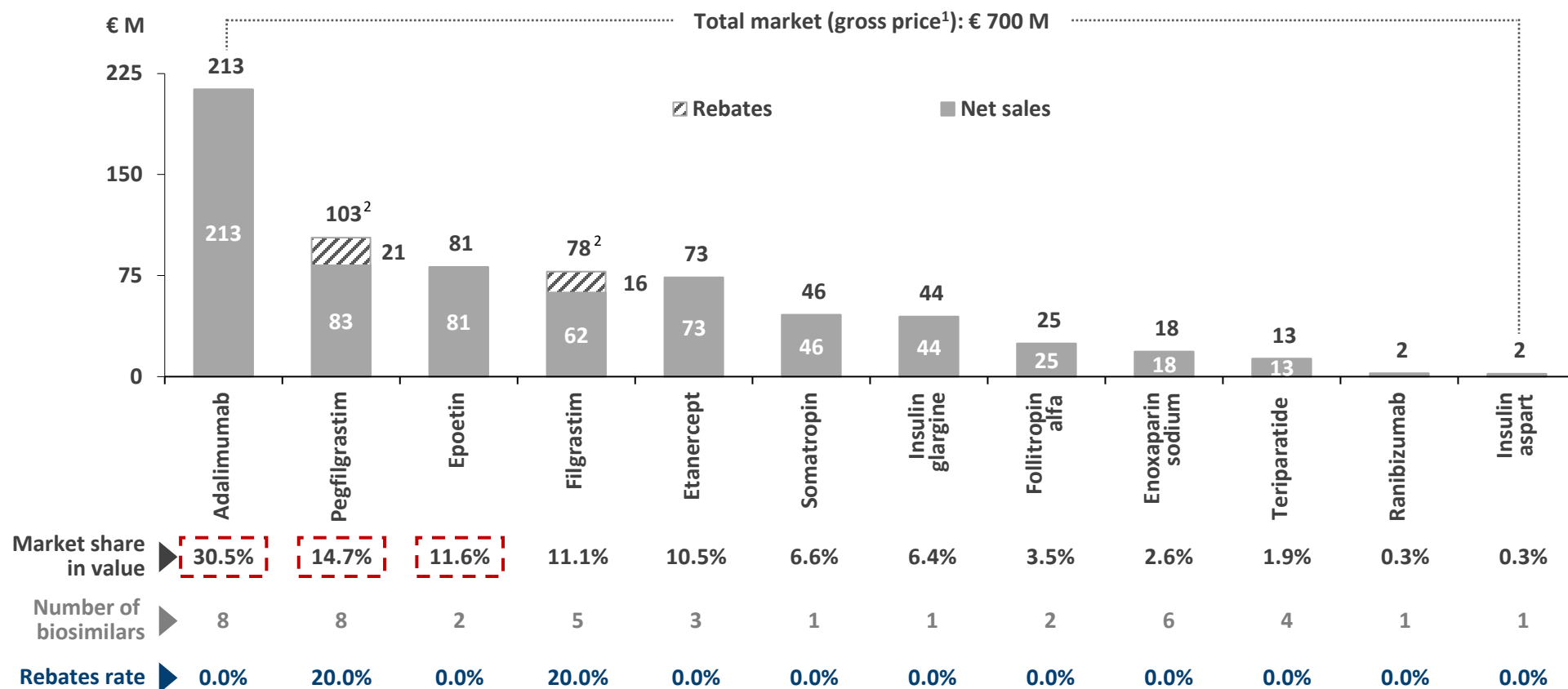


Sources: ANSM – GERS (December 2023) – Smart Pharma Consulting analyses

¹ Since December 2023. Previously marketed by Viatrix – ² Belonging to Fresenius Kabi but marketed by Teva

In 2023, adalimumab, pegfilgrastim and epoetin led the French biosimilars retail market, accounting together for ~57% of the market in value

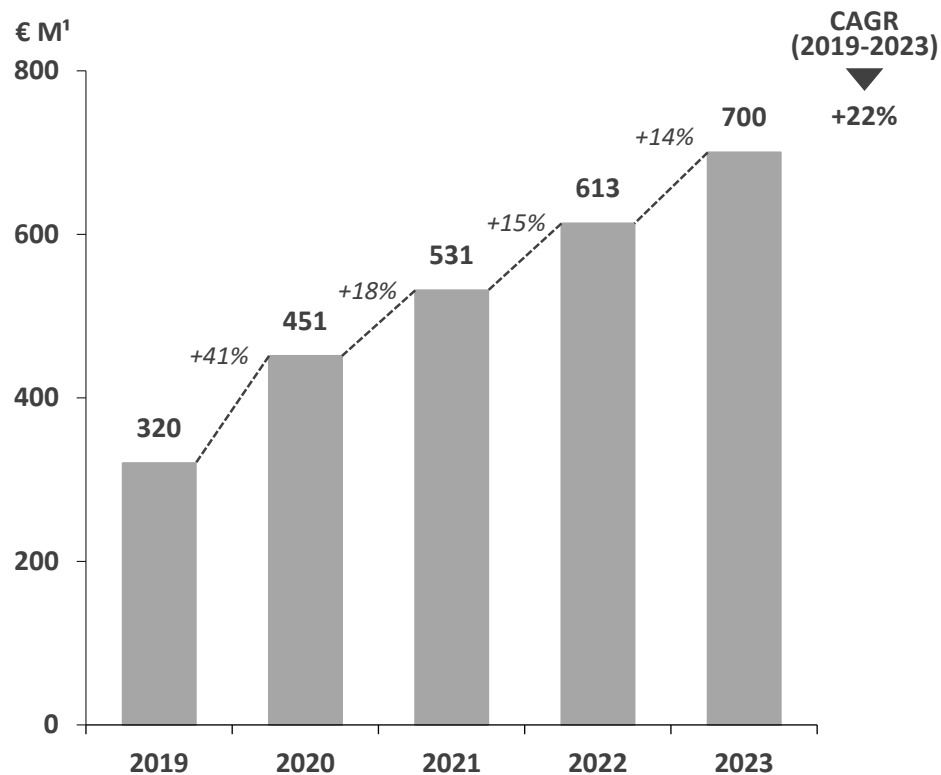
Retail biosimilars market size (2023)



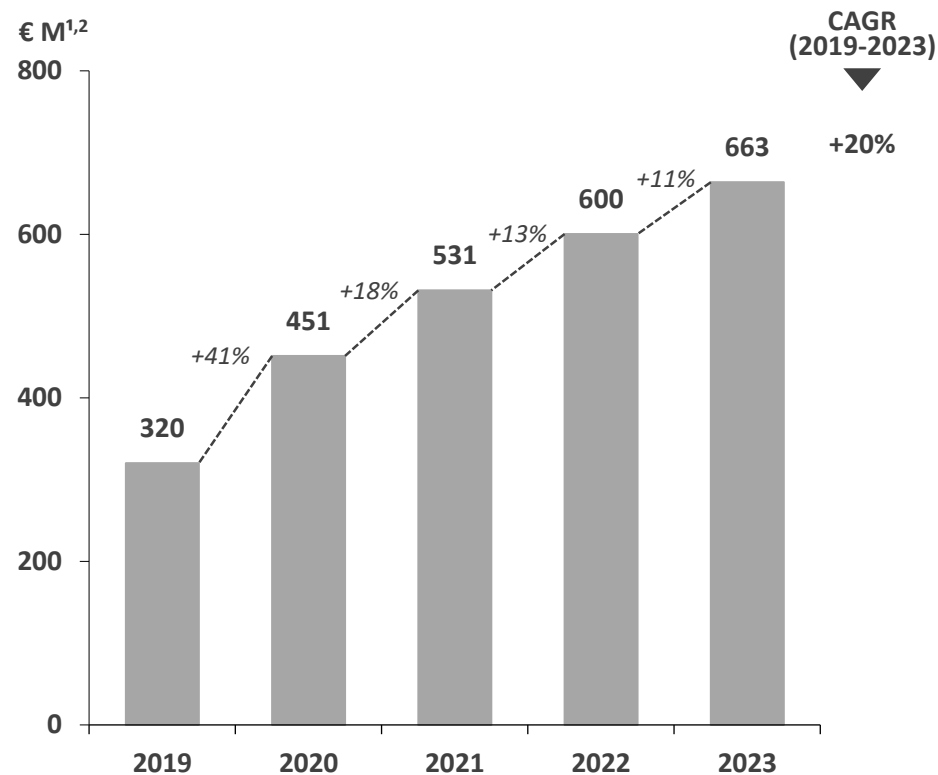
In 2023, biosimilars retail sales reached € 700 M in gross value and an estimated € 663 M in net value, representing a +22% and a +20% CAGR between 2019 and 2023, respectively

Retail biosimilars market evolution (2019 – 2023)

Gross price



Net price



Sources: GERS (December 2023) – Smart Pharma Consulting analyses

¹ Ex-factory prices before taxes – ² Assuming the following discounts on biologics substitutable (i.e., filgrastim and pegfilgrastim): 10% from April 2022 to December 2022 and 20% in 2023

In April 2024, the price difference between original biologics and their biosimilars ranges from -32.9% (for pegfilgrastim) to +11.9% (for epoetin)

Price differences between retail original biologics and biosimilars (2024)

INN	Original biologics	Date of 1 st biosimilar commercialization	Original biologic price ¹ in € (April 24)	Biosimilar price ¹ in € (April 24)	Price difference (April 24)
Pegfilgrastim	Neulasta (Amgen)	November 2018	594.78	399.13	-32.9%
Follitropin alfa	Gonal-F (Merck)	May 2015	194.88	139.49	-28.4%
Ranibizumab	Lucentis (Novartis)	March 2023	377.78	283.34	-25.0%
Tocilizumab	Roactmera (Roche)	Feb. 2024	589.72	442.29	-25.0%
Insulin aspart	Novorapid (NovoNordisk)	March 2021	12.27	9.60	-21.8%
Adalimumab	Humira (AbbVie)	October 2018	438.96	367.95	-16.2%
Somatropin	Genotonorm (Pfizer)	June 2008	1,290.57	1,134.04	-12.1%
Filgrastim	Neupogen (Amgen)	November 2009	54.58	50.49	-7.5%
Enoxaparin	Lovenox (Sanofi)	September 2018	22.98	22.06	-4.0%
Insulin glargine	Lantus (Sanofi)	January 2016	32.44	31.51	-2.9%
Teriparatide	Forsteo (Lilly)	August 2019	176.18	172.73	-2.0%
Etanercept	Enbrel (Pfizer)	October 2016	466.85	457.76	-1.9%
Epoetin	Eprex (Janssen)	July 2008	153.21	171.42	+11.9%

Sources: National Health Insurance tariffs (April 2024) – Smart Pharma Consulting analyses

¹ For each INN, unit ex-factory price before discounts and taxes of the most sold SKU in 2023 – ² The fact that the original biologic has a higher price than its biosimilars results from Janssen pricing strategy to encourage physicians to remain loyal to their brand and to the negotiation with the CEPS. However, this gap should be reduced in the short-term since the CEPS is currently negotiating a price decrease for the corresponding biosimilars of Sandoz and Pfizer

The ANSM has established a provisional timetable of the similar biologic groups they have to assess and give an opinion regarding their substitutability at retail pharmacy level

Assessment of biosimilars' substitutability by the ANSM – 2024 Timetable¹

Timetable	INN	Indications	Original Biologics	Biosimilars
Q1	Teriparatide	Osteoporosis	Forsteo (Lilly)	Livogiva – Movymia – Sondelbay – Terrosa
	Eculizumab*	PNH ²	Soliris (Alexion)	Bekemv – Epysqli
	Ranibizumab	AMD ³	Lucentis (Novartis)	Ranivisio – Byooviz – Ximluci
Q1 / Q2	Enoxaparin	Angina – infarction – DVT ⁴	Lovenox (Sanofi)	Enoxaparin Arrow – Enoxaparin Becat – Enoxaparin Biogaran – Enoxaparin Crusia – Enoxaparin Teva – Inhixa
Q2 / Q3	Adalimumab	RA ⁵ – Psoriasis – IBD ⁶	Humira (AbbVie)	Amgevita – Amsparity – Hukyndra – Hulio – Hyrimoz – Idacio – Imraldi – Yuflyma
	Etanercept	RA – Psoriasis	Enbrel (Pfizer)	Benepali – Erelzi – Nepexto
	Rituximab*	Rheumatoid arthritis	MabThera (Roche)	Rixathon – Ruxience – Truxima
	Insulin aspart	Diabetes	Novorapid (NN ⁷)	Insulin aspart Sanofi
	Insulin glargine		Lantus (Sanofi)	Abasaglar
	Insulin lispro		Humalog (Lilly)	No Bx launched
	Epoetin	Cancer – CKD ⁸	Eprex (Janssen)	Binocrit – Retacrit
	Follitropin α	Functional anovulation	Gonal-F (Merck)	Bemfola – Ovaleap

* Have been included by error since they are hospital-only drug, not sold by retail pharmacists

Sources: ANSM – SmPCs – Smart Pharma Consulting analyses

¹ Aflibercept and tocilizumab biosimilars have been added to the biosimilars repertory on December 29, 2023, and are not to be assessed this year

– ² Paroxysmal nocturnal hemoglobinuria – ³ Wet age-related macular degeneration – ⁴ Deep vein thrombosis – ⁵ Rheumatoid arthritis –

⁶ Inflammatory bowel disease including Crohn's disease and ulcerative colitis – ⁷ Novo Nordisk – ⁸ Chronic kidney disease

All the biologics assessed by the ANSM should become substitutable but with restrictions for some of them, while certain prescribers will write “No substitution” on their prescription

Retail market: Estimates of substitutability barriers

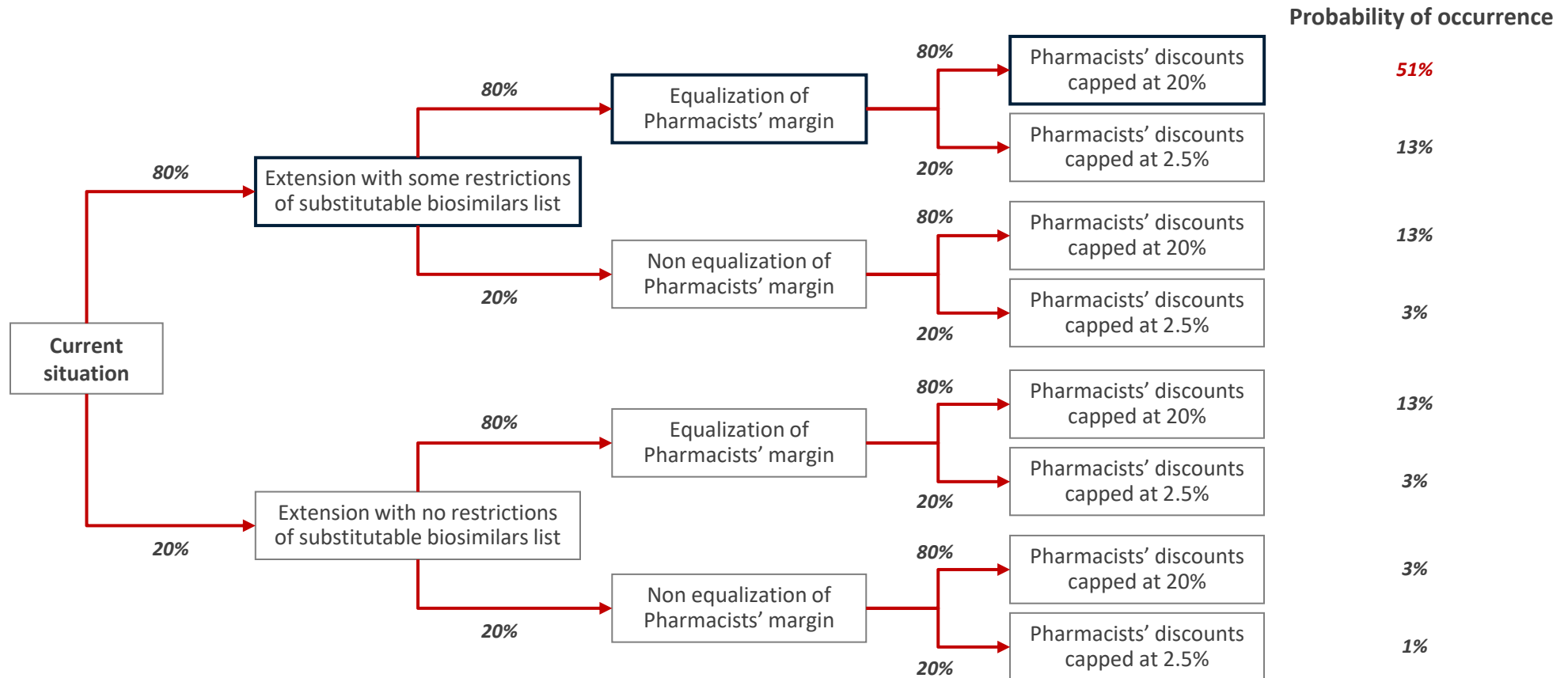
INN	Treatment duration	Forms / dosages differences	Physicians' positions		ANSM position re. substitutability	Bx penetration dynamics
			Bx prescription ¹	Substitution		
Adalimumab	2-3 years	Different dosages / pack size / excipients	59%	At initiation	Restricted to initiations	Limited acceleration
Enoxaparin	5 to 35 days	Not all dosages	18%	No objection	Allowed	High acceleration
Epoetin	≥ 4 months	Similar injector Same dosage	82%	Not in nephrology	Allowed	Limited acceleration
Etanercept	2-3 years	Different dosages	57%	At initiation	Restricted to initiations	Limited acceleration
Follitropin α	4 months	Different injectors Different dosages	51%	Not favorable ³	Restricted to initiations	No acceleration
Insulin aspart	Life-long	Different injectors (pen – cartridge)	35%	No objection	Allowed	Medium acceleration
Insulin glargine	Life-long	Similar injector Same dosage	48%	No objection	Allowed	Medium acceleration
Insulin lispro	Life-long	NA	Bx not marketed	No objection	Allowed	Medium acceleration
Ranibizumab	Several years	Different injectors (PFS – injectable solution)	4% ²	If as convenient ⁴	Allowed	Limited acceleration
Teriparatide	≤ 18 months	Pen with or without cartridge	52%	No objection	Allowed	Medium acceleration

Sources: GERS data – EMA – ANSM – Vidal (April 2024) – Key stakeholders' interviews – Smart Pharma Consulting analyses

¹ As of December 2023 in standard units – ² Recently launched – ³ Success rate of 30% only for IVF (In-Vitro Fertilization) – ⁴ Injected by prescribers who in general run after time

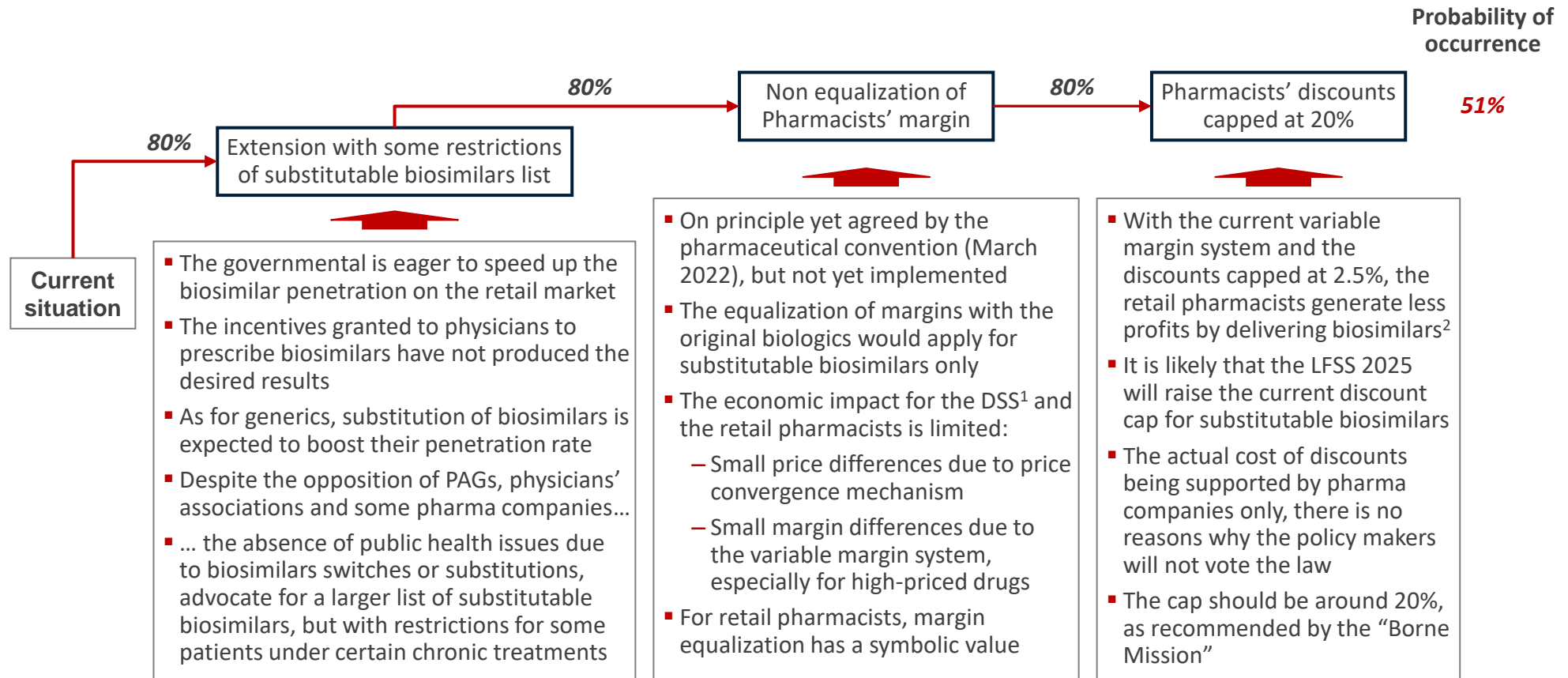
Based on market research and analysis, we assume that most of biosimilars, with restrictions for some of them will be substitutable, margins will be equalized, and discount capped at ~20%

Market changes driven by health authorities – Scenario building (2024 – 2027)



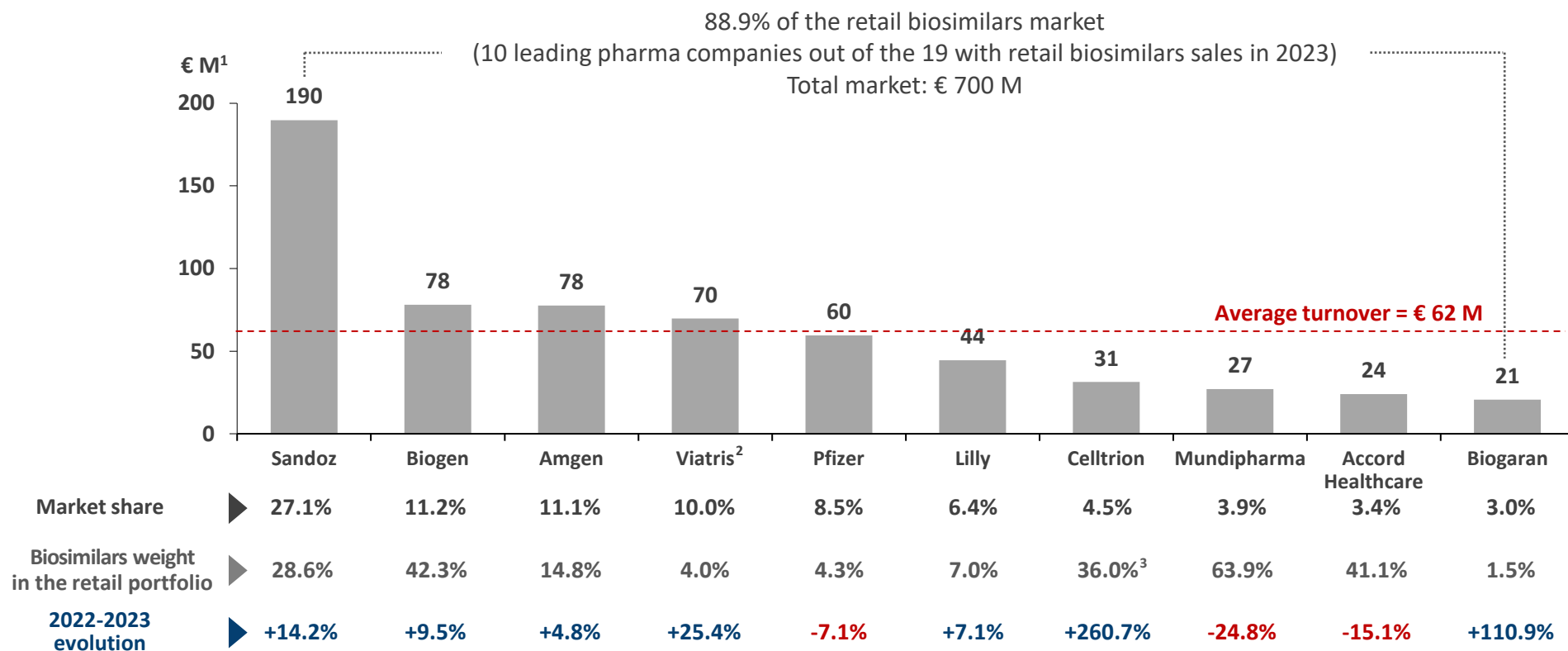
Based on market research and analysis, we assume that most of biosimilars, with restrictions for some of them will be substitutable, margins will be equalized, and discount capped at ~20%

Retail market: Rationale supporting the most likely market scenario



In 2023, Sandoz, Biogen, Amgen and Viatris generated individually € 70 M or more retail sales and represented together ~59% of the French retail biosimilars market in value

Top 10 companies on the retail biosimilars market – In value (2023)



Note: Other companies operating on the French biosimilars market as of April 2024: Arrow, EG Labo, Fresenius Kabi, Gedeon Richter, Rovi, Samsung Bioepis, Sanofi, Teva, Theramex and Zentiva

14 of the biosimilars players have a weak competitive position at retail pharmacies, the two best established ones have a limited portfolio, while Sandoz and Teva have well balanced position

Mapping of pharma companies marketing biosimilars in the retail market

Number of proposed Biosimilars ¹	6		Sandoz	
	5			
	4	Pfizer	Teva	
	3	Accord Healthcare Biogen	Biocon	Biogaran
	2	Fresenius Kabi Sanofi Theramex	Arrow EG Labo	
	1	Amgen Mundipharma Rovi	Celltrion Gedeon Richter Lilly Samsung Bioepis	Zentiva Viatrix
		Weak	Medium	Strong
Competitive position at retail pharmacy level				

R&D-based companies – Generics and/or biosimilars companies – Mature brand companies

Sources: Smart Pharma Consulting analyses

¹ As of April 2024

The development of the substitutable biosimilars market segment will lead to important challenges irrespective of the group the pharma companies belong to

Typology of pharma companies marketing biosimilars

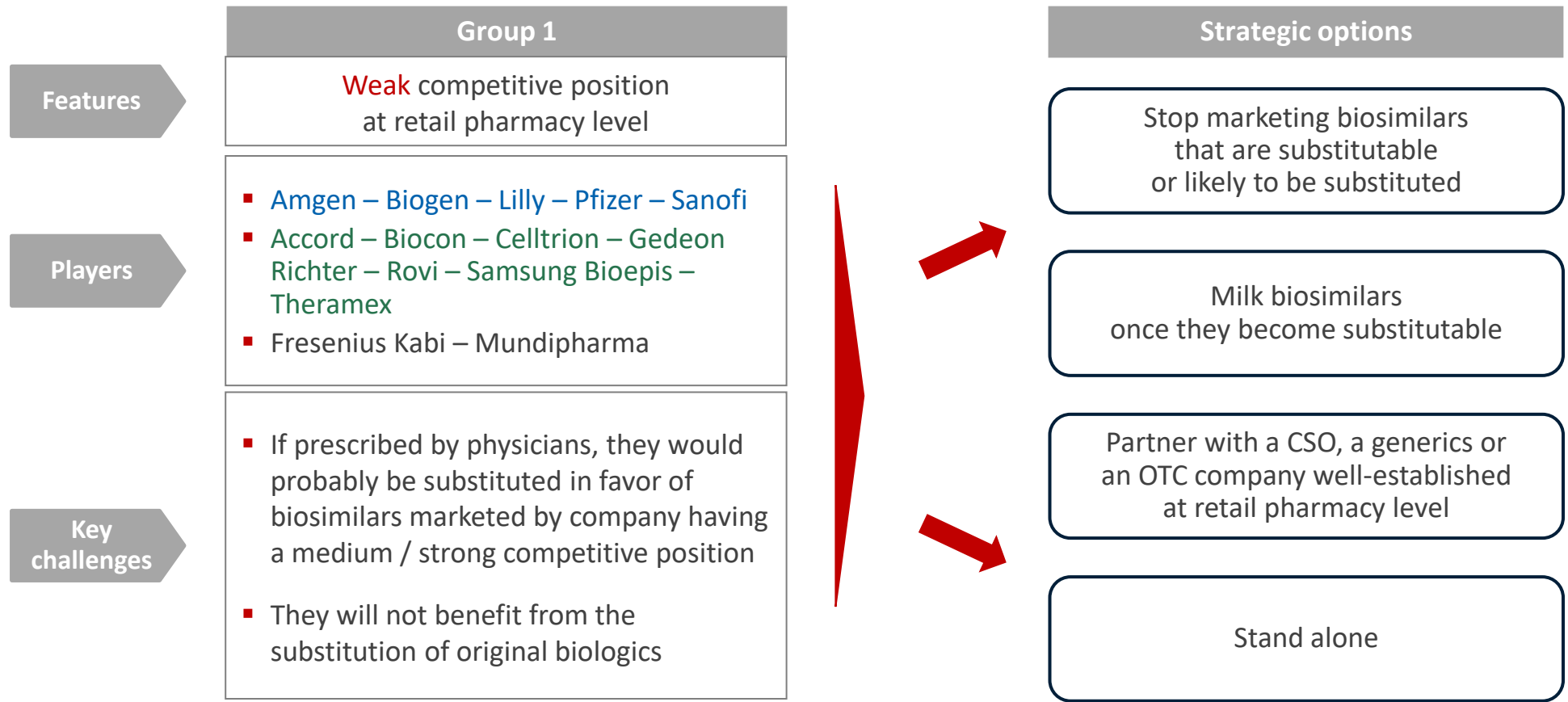
	Group 1	Group 2	Group 3
Features	Weak competitive position at retail pharmacy level	Medium competitive position at retail pharmacy level	Strong competitive position at retail pharmacy level
Players	<ul style="list-style-type: none"> Amgen – Biogen – Lilly – Pfizer – Sanofi Accord – Biocon – Celltrion – Gedeon Richter – Rovi – Samsung Bioepis – Theramex Fresenius Kabi – Mundipharma 	<ul style="list-style-type: none"> Arrow EG Labo Sandoz Teva Zentiva 	<ul style="list-style-type: none"> Biogaran Viatrix
Key challenges	<ul style="list-style-type: none"> If prescribed by physicians, they would probably be substituted in favor of biosimilars marketed by company having a medium / strong competitive position at retail pharmacies' level They will not benefit from the substitution of original biologics 	<ul style="list-style-type: none"> The companies with a broader portfolio (e.g., Sandoz, Teva) are well-positioned to reinforce their competitive position at retail pharmacies' level Those with a narrow portfolio will be at risk on both their generics and biosimilars businesses 	<ul style="list-style-type: none"> They cannot take advantage of their strong position due to their limited biosimilars portfolio Could be “attacked” on the generics business by companies with a medium competitive position but a broader biosimilars portfolio

R&D-based companies – Generics and/or biosimilars companies – Mature brand companies

Sources: Smart Pharma Consulting analyses

To keep on playing on the retail substitutable biosimilars market,
 Group 1 pharma companies should partner with retail pharmacies, through third parties

Group 1: Strategic options

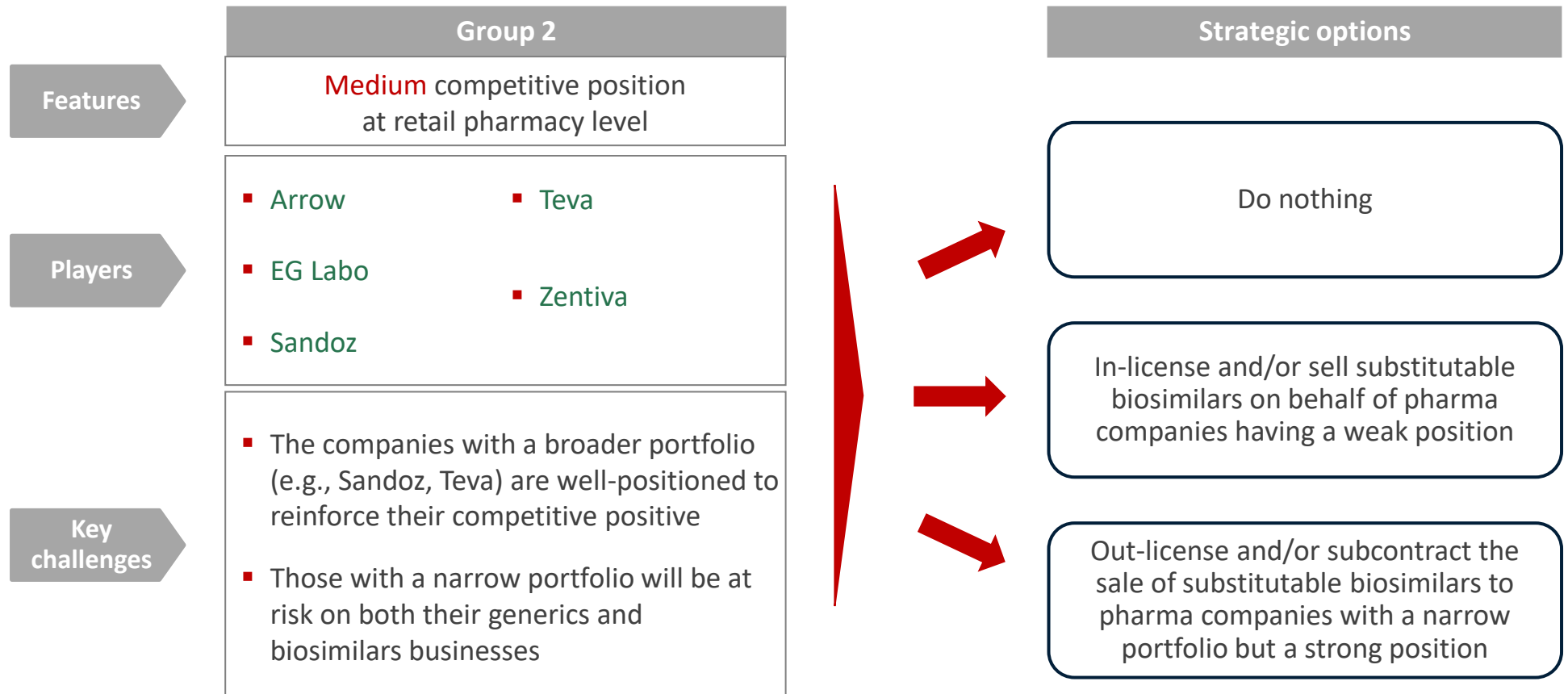


R&D-based companies – Generics and/or biosimilars companies – Mature brand companies

Sources: Smart Pharma Consulting analyses

The strategy of Group 2 pharma companies will depend on the size of their portfolio, and their ability and willingness or not to be a leading player on the substitutable biosimilars market

Group 2: Strategic options

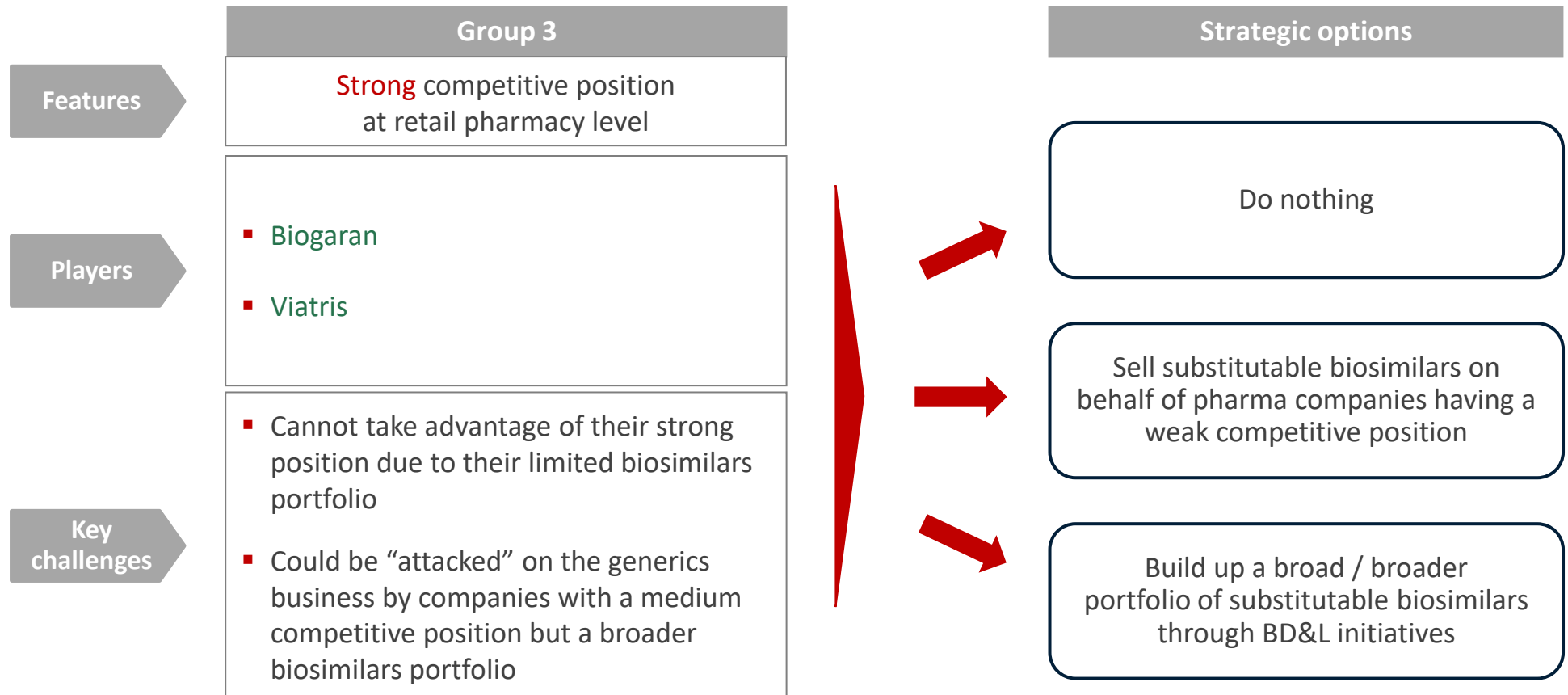


R&D-based companies – Generics and/or biosimilars companies – Mature brand companies

Sources: Smart Pharma Consulting analyses

To remain competitive on the retail substitutable biosimilars market, Group 3 pharma companies should either sell on behalf of, or in-license from, biosimilars manufacturers

Group 3: Strategic options

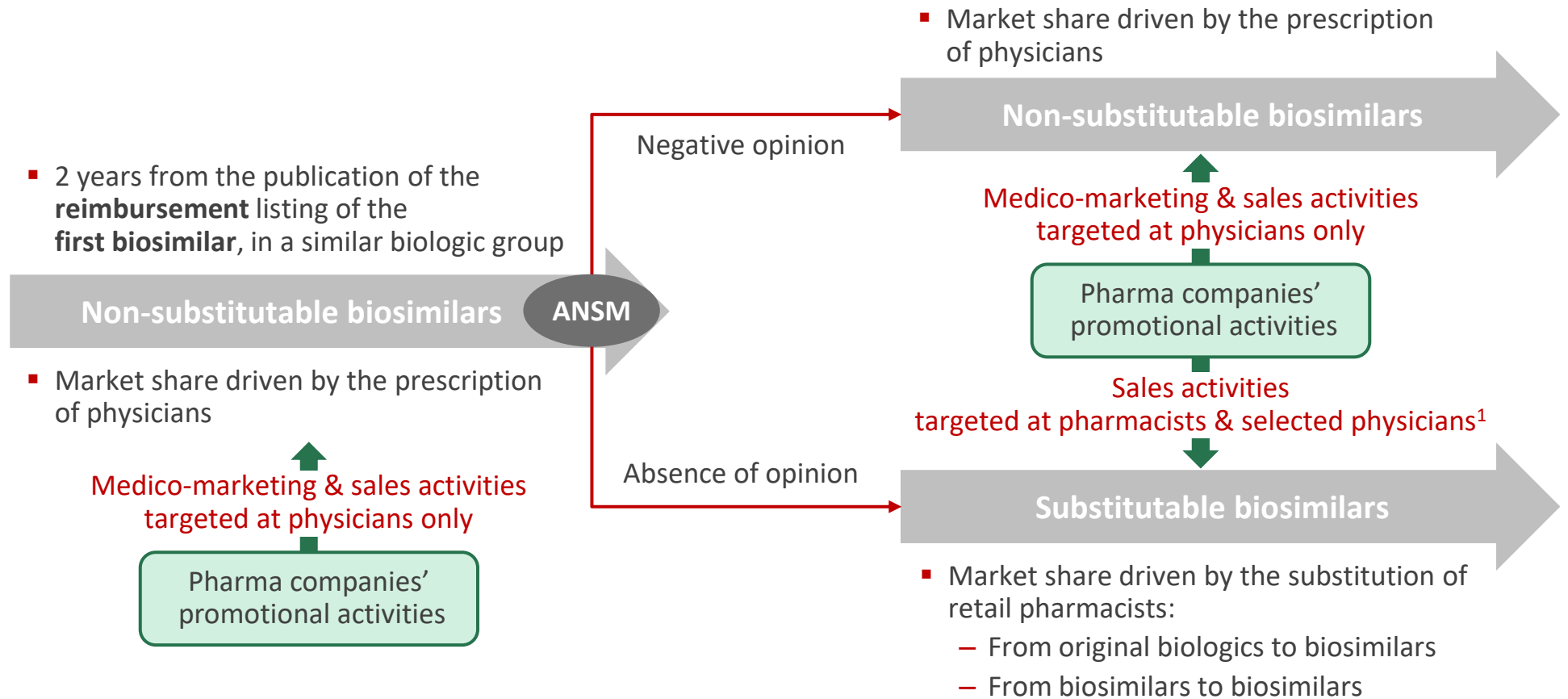


R&D-based companies – Generics and/or biosimilars companies – Mature brand companies

Sources: Smart Pharma Consulting analyses

Pharma companies will require medical reps only to promote non-substitutable biosimilars to physicians and pharmacy reps only to sell substitutable biosimilars to retail pharmacists

Biosimilars substitutability: Implications for pharma companies (1/2)



The sales activities of pharma companies at retail pharmacists should not start before the biosimilars become substitutable

Biosimilars substitutability: Implications for pharma companies (2/2)

	Physicians	Pharmacists
Non substitutable phase	<ul style="list-style-type: none"> Promotional activity at targeted physicians... ... to strengthen physicians' preference for the marketed biosimilars 	NO ACTION
Substitutable phase	<ul style="list-style-type: none"> Promotional activity stopped... ... or restricted to physicians who are opposed to biosimilars' substitution... ... and willing to prevent substitution by indicating on their prescription, next to the name of the biologic¹ prescribed, "Non-substitutable" 	<ul style="list-style-type: none"> Sales activity to get the biosimilar listed... ... and preferentially substituted at the expense of the original biologic or of another biosimilar

The optimal strategies of pharma companies marketing biosimilars would depend on their competitive position at retail pharmacies, each product status and the diseases it addresses

Key Takeaways

1. Regulatory environment

- Filgrastim and pegfilgrastim are substitutable since April 2022
- From 2024 onwards, expansion of the list with existing drugs¹
- For new biosimilars, a period of 2 years will precede the possibility to substitute biologics¹

3. Pharmacists' behavioral trends

- Pharmacists do not anticipate difficulties to substitute biologics for naïve patients
- For patients under a chronic therapy, they will substitute depending on each patient
- If opportunities to substitute are rare, pharmacists should not be very pro-active



2. Physicians' behavioral trends

- Physicians, especially hospital-based, are used to initiate treatments with biosimilars...
- ... but are more reserved regarding switching and substituting chronic treatments when patients' disease is well controlled²

4. Patients' behavioral trends

- Naïve patients should in large proportion accept biosimilar substitution, but...
- ... if yet treated and well-controlled, they will have to be convinced by pharmacists
- Even if they accept, they may have trouble to adjust if the delivery device is different

5. Pharma companies' strategic options & recommendations

- During the two years before biosimilars become substitutable, they should be promoted to physicians³
- Certain substitutable biosimilars should still be promoted³
- Agreements with retail pharmacists and VTOs⁴ they belong to, are essential to succeed on the biosimilar substitutable market
- To do so, company marketing biosimilars strategies would depend on their competition position at retail pharmacies:
 - If weak: partner with a company yet well-established, a CSO⁵ or leave the market
 - If medium: in-license or sell biosimilars of companies having a weak position or out-license / subcontract to a 3rd party having a strong position
 - If strong: pharma companies should either sell on behalf of, or in-license from, biosimilars manufacturers

Consulting firm dedicated to the pharmaceutical sector operating
in the complementary domains of strategy, management and organization

Market Insights Series

- The Market Insights Series has in common to:
 - Be well-documented with recent facts and figures
 - Highlight key points to better understand the situations
 - Determine implications for key stakeholders
- Each issue is designed to be read in 15 to 20 minutes and not to exceed 24 pages

Biosimilars Substitution Impact

Situation Analysis & Strategic Options

This position paper analyzes the current market segment situation and estimates its perspectives of evolution

Thus, the following topics are covered:

- Regulatory framework
- Key stakeholders' analysis (health authorities – healthcare professionals – pharma companies)
- Scenario building and likely impacts
- Strategic options assessment
- Recommendations

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Best regards

Jean-Michel Peny