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Biosimilars: Commercial Perspective

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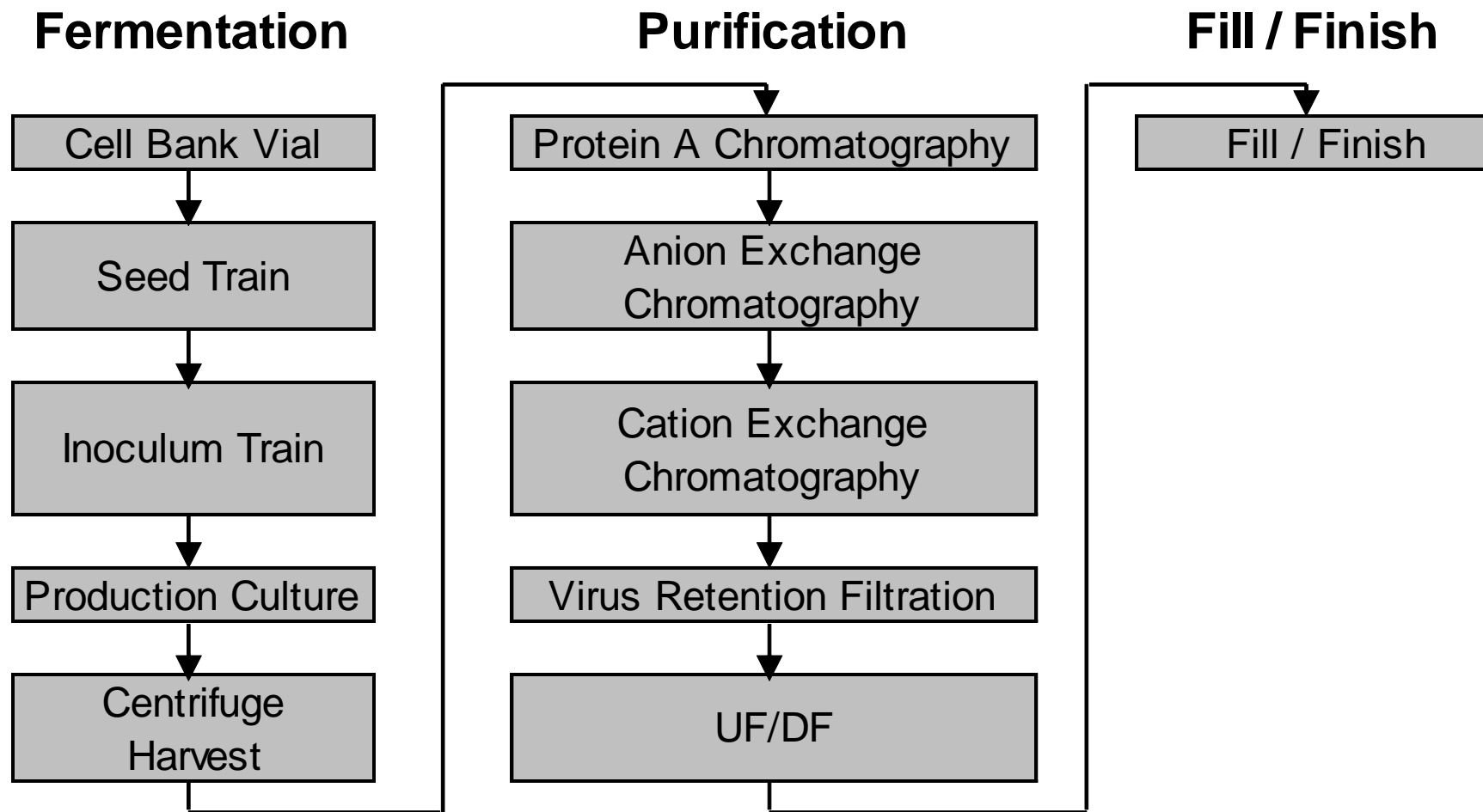
Three topics

Commercial rationale for biosimilars

Adoption in Europe

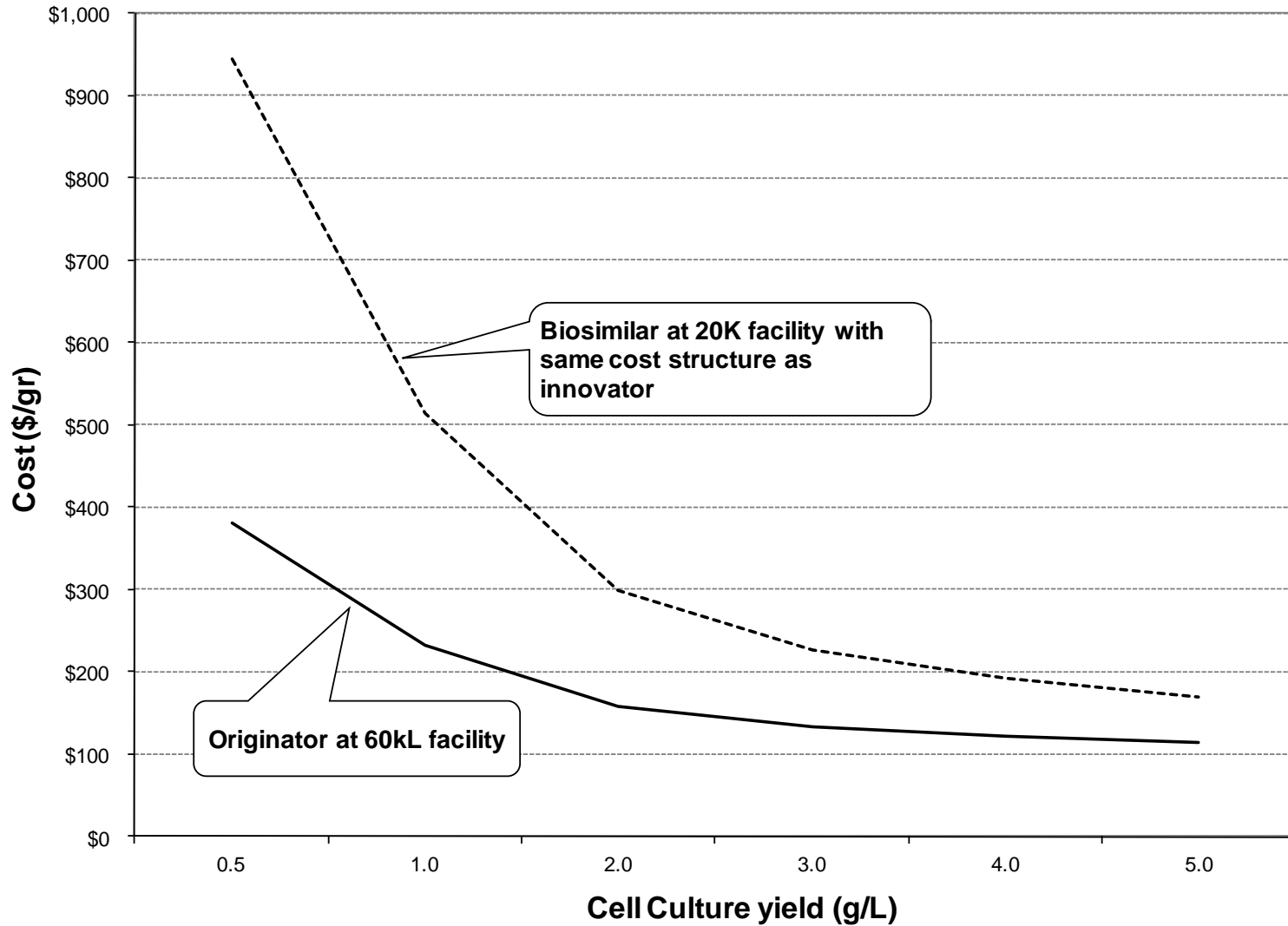
Emerging US dynamics

The manufacturing process of proteins, particularly antibodies was standardized over the past two decades



Classic Iterative 'Standing On The Shoulders Of Giants' Improvement

...Resulting in substantial savings in the cost of manufacturing



Source: Industry interviews; Bernstein analysis; notes Initial biosimilar yield may be inferior to innovator yield due to need to match reference material; some innovators' costs are now <\$100/gram

The difference between manufacturing cost and (rising) price led to very high gross margins

Product	Price	price/g	Manufacturing Cost Assuming 2 g/L yield (\$/gr)*	Cost / Price*
Avastin	\$687.5/ 100mg	\$6,875	\$188	2.7%
Enbrel	\$243 / 25mg	\$9,706	\$428	4.4%
Remicade	\$784 / 100mg	\$7,839	\$188	2.4%
Humira	\$1,816 / 40mg	\$45,400	\$308	0.7%
Rituxan	\$675 / 100mg	\$6,751	\$188	2.8%
Herceptin	\$3,331 / 440mg	\$7,570	\$126	1.7%
Erbitux	\$600 / 100mg	\$6,000	\$188	3.1%
Soliris	\$5122 / 300mg	\$17,073	\$135	0.8%
Average	1657.3125	\$12,877	\$231	2.3%

Falling barriers and increasing profits attract competition

Source: Bernstein analysis, market data as of 4Q2008; note: IP licensing is excluded from cost calculation. Calculation intends to show direct gross margin of innovators. Cost of sales and marketing and discount given by biosimilars not included.

Summary: the dawn of 'biosimilar/follow-on age' is driven by the natural progression of knowledge and economics

- We all owe a debt of gratitude to Pfizer and Roche (or more correctly their preceding companies) for taking antibody manufacturing from an art to a science.
- Now, (i) technology is much more available; (ii) coupled with very high originator profits, and (iii) requires only moderate upfront investment (e.g. \$100-\$200M per drug).
 - This combination attracts additional competition – the laws of economics
- Two side benefits:
 - Originators are forced to innovate to stay ahead of competition
 - Innovation in manufacturing as costs become more important

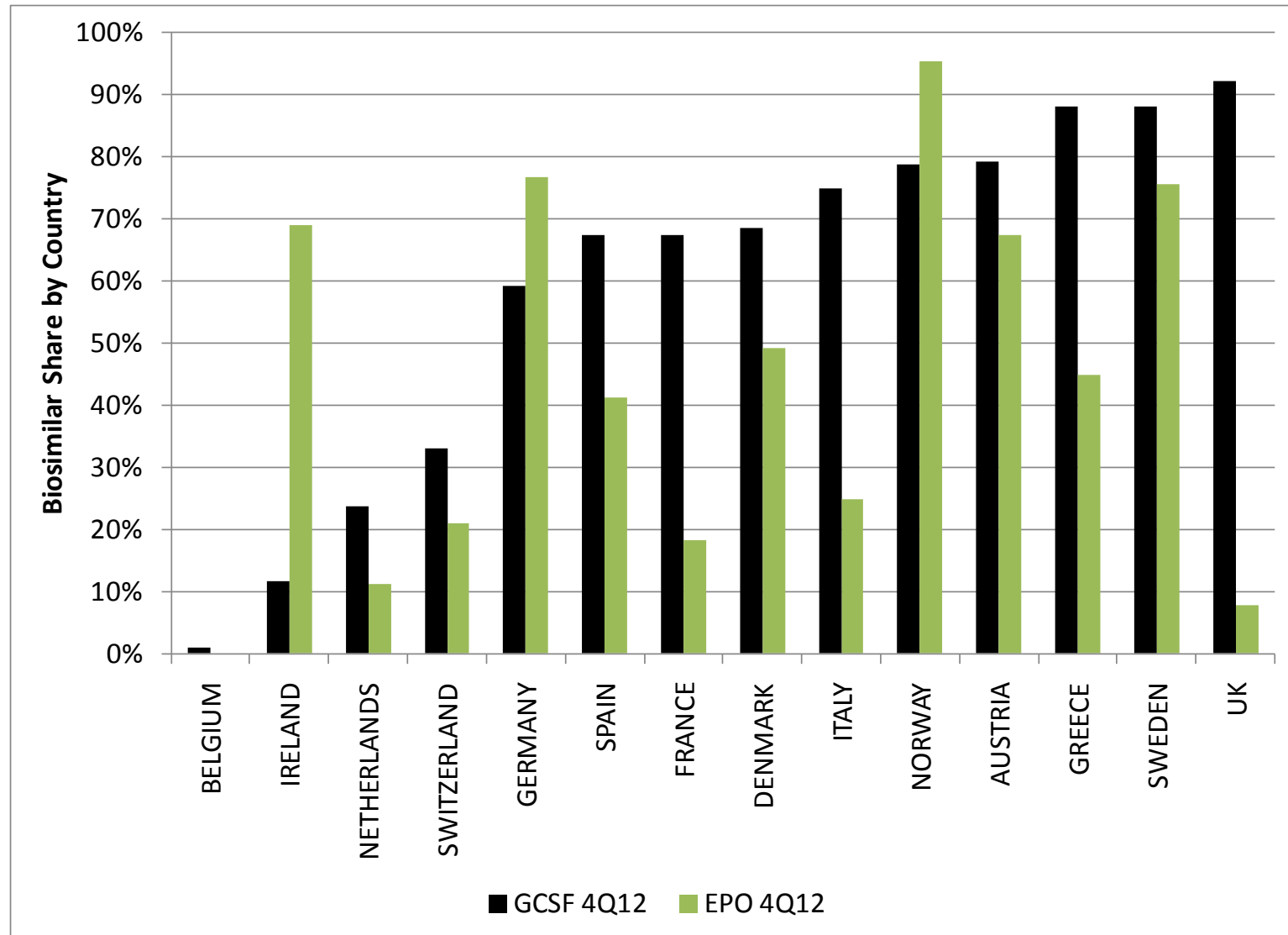
Three Topics

Commercial rationale for biosimilars

Adoption in Europe

Emerging US dynamics

Adoption of biosimilars is critically dependent on market infrastructure; varies significantly between countries



Source: market interviews

EU adoption generally correlated to strength of generic adoption frameworks

Germany

High Adoption

- Most biosimilars originated locally; more favorable view of biosimilar quality
- Governments encourage biosimilars with quota requirements
- Hospitals are paid by disease code and use biosim's saving elsewhere; independent prescribers have drug budgets

United Kingdom

High Adoption

- Physicians are public employees, prescribe to NICE guidelines
- Products are purchased in tenders by HC trusts; price 50% of tender equation

France

Variable Adoption

- Hospitals are highly incentivized to use biosimilars; physicians' incentives not strong

Spain

Variable Adoption

- Physicians historically have limited incentives to be cost conscious; situation is changing with financial crisis; varies by region

Italy

Variable Adoption

- Physicians historically have limited incentives to be cost conscious; situation is changing with financial crisis; varies by region

Source: interviews; Bernstein analysis

Three Topics

Commercial rationale for biosimilars

Adoption in Europe

Emerging US dynamics

Multiple credible companies are participating in the market

	Oncology				aTNF			Others
	Herceptin (trastuzumab) Roche	Avastin (bevacizumab) Roche	Rituxan (rituximab) Roche / Biogen Idec	Erbix (cetuximab) BMS / Merck KGaA	Humira (adalimumab) AbbVie	Enbrel (etanercept) Amgen / Pfizer	Remicade (infliximab) J&J / Merck	Synagis
Novartis / Sandoz	p1	Preclinical	p3		Preclinical	p3	Preclinical	
Hospira / Celltrion	p3 (Jun-13)	Preclinical	p3 stopped p1 HSP alone	Preclinical	Preclinical		Approved	Preclinical
Pfizer	p1 (Nov-12)	p1	p1/p2 RA	Preclinical	p1		p1 (Oct-13)	
Actavis/ Amgen	p3 paused Sept. 2015	p1	Preclinical	Pre-clinical	p1		Preclinical	
Boehringer Ingelheim		p1 (Nov-12)	p3 RA/FL		p1 (Jul-12)			
Mylan/Biocon	p3 started	Preclinical			Preclinical	Preclinical		
Baxter/ Momenta	Preclinical				Preclinical		Preclinical	
Merck KGaA / Reddy	Preclinical		p1					
Merck - Samsung Bioepis			p1/p3			p3		
Richter	Preclinical		Preclinical	Preclinical				

Source: FDA, EMA, Industry discussion, SCB analysis; mid 2013 view. Additional programs likely exist but are undisclosed

Success, however, is uncertain. We see substantial pre-launch barriers

Reference material
availability

Innovators can restrict availability of reference material via REMS programs or exclusive pharmacy networks

IP

Unlike small molecules, biologics patent-book not 'cleaned' by decades of litigation; risk of secondary patents, need for orange book-like system

Challenge the law or
product approach

Challenges to law and FDA interpretation of it; challenge FDA approach to approve individual products (CP and law); Late process intervention

REMS

Limit access to REMS program, increase sophistication – e.g. Suboxone

Source: Company disclosures, Expert conversations, SCB Analysis

Post approval commercial barriers look particularly formidable

Lack of payer incentive

Misaligned incentives – examples (i) value of rebates in LTC formulary; (ii) lack of incentive in PDP

Lack of physician incentive

(i) With a few exceptions physicians have less to gain from using biosimilars. (ii) “why would you ever switch a patient away from gold Standard”. (iii) “Would you buy from a generic company or from one who supports developing new drugs for your specialty”

Lack of patient incentive

No benefit from switching, risk of losing wrapped services. Often isolated from copay or coinsurance

First Dose

Chronic drugs often very cheap at facilities which usually provide ‘first dose’ (e.g. Hospitals). Challenging to switch patients afterwards. Particularly if state legislatures restrict it

Rebate Trap

Rebates can reach 50% of list price. For every patient retained on reference product, cost is 2x. Could kill adoption of biosimilars in chronic treatment if states do not allow switching existing patients

Boots on the ground

Pharma will reargue the logic of biosimilars approvability with each doctor “inferior clinical package”; biosimilars can’t match the innovator reach

Professional societies

Often close relations or funded by innovators; recommending bodies can support or resist biosimilars. E.g. use of Neupogen in healthy volunteers in EU

Service wrapper

Innovators have direct-to-patient services; costs (inc. copay assistance) can reach 20% of drug revenue. A conflict of interest for channel company which own specialty pharmacies

Example 1: Using rebate as commercial barriers

Rebate Trap

Rebates can reach 50% of list price. For every patient retained on reference product, cost is 2x. Could kill adoption of biosimilars in chronic treatment if states do not allow switching existing patients

Pre biosimilar

List price of innovator drug for PBM: \$10,000;
Post rebate innovator price: \$5,000
Patients: 1,000

Payor cost: \$5,000,000

Biosimilar enters:

- Offers **60%** price discount off the rebated price
- Payor adopts biosimilar as first option; loses rebate
- 50% of patients switch
- Payor loses money; biosimilar fails

With biosimilar

List price of Innovator drug for PBM: \$10,000;
No rebate innovator price: \$10,000
Patients: 500
+
Price of biosimilar: \$2,000
Patients: 500

Payor Cost:

Patients on innovator drug: \$5,000,000
+ Patients on biosimilar: \$1,000,000
\$6,000,000

Successful introduction of biosimilar in the presence of high rebate originator requires near complete switch, grandfathering existing patients implies failure of low cost option

Example 2: Capturing the first dose

First Dose

Chronic drugs often very cheap at facilities which usually provide 'first dose' (e.g. Hospitals, LTC). Challenging to switch patients afterwards. Particularly if state legislatures restrict it.

Patient exits hospital to LTC facility under Medicare part A; provider receives capitated pay for stay; sensitive to cost of drug

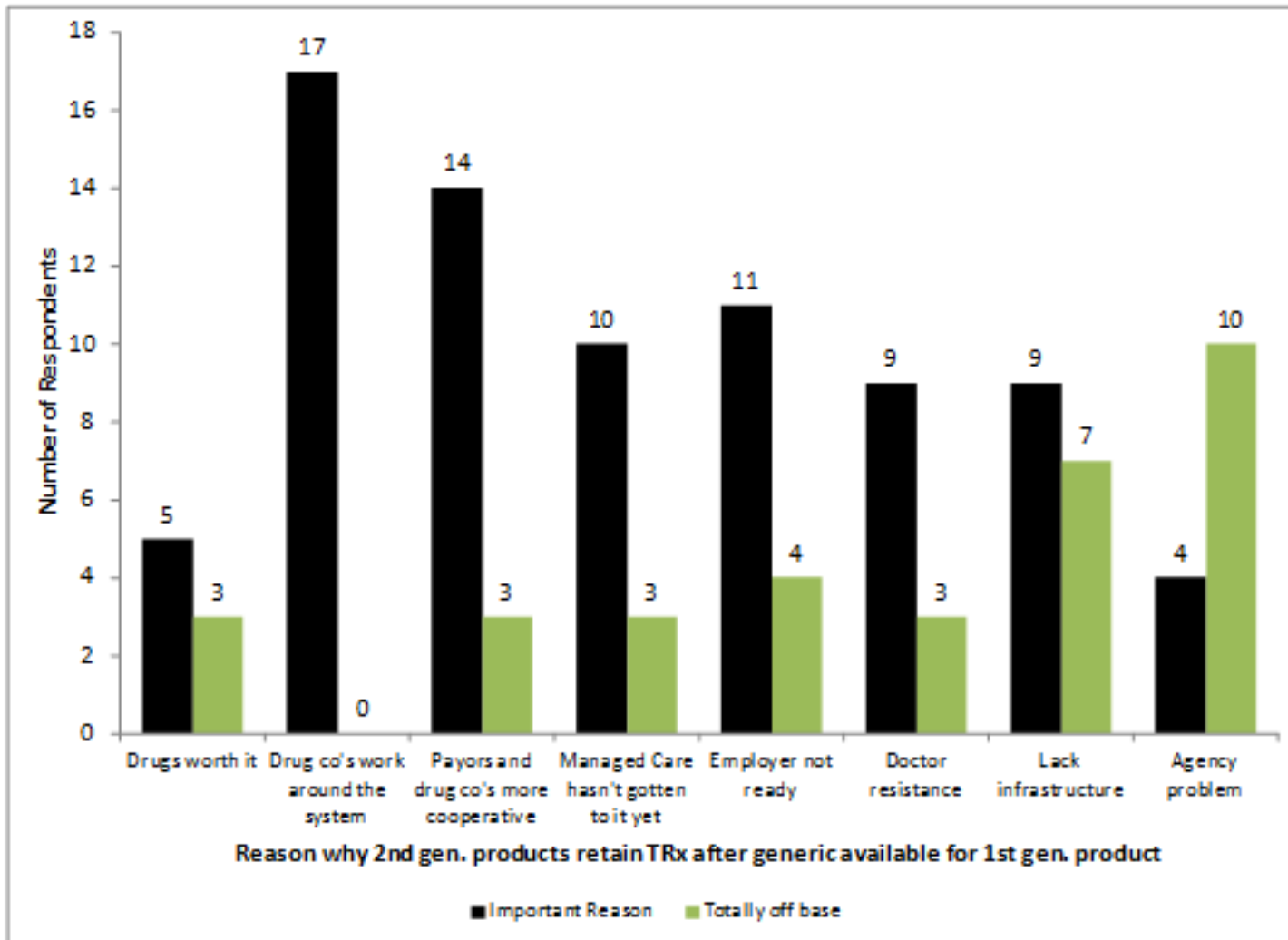
Innovator provides drug at deep discount to LTC; competing on price with biosimilar; relies on position as 'gold standard' and relationships to establish treatment on its drug

Patient exit LTC and goes home; already using innovator product

In home setting (PDP), price gap may exist between biosimilar and innovator drug, but it is now a switch, not a new patient start...

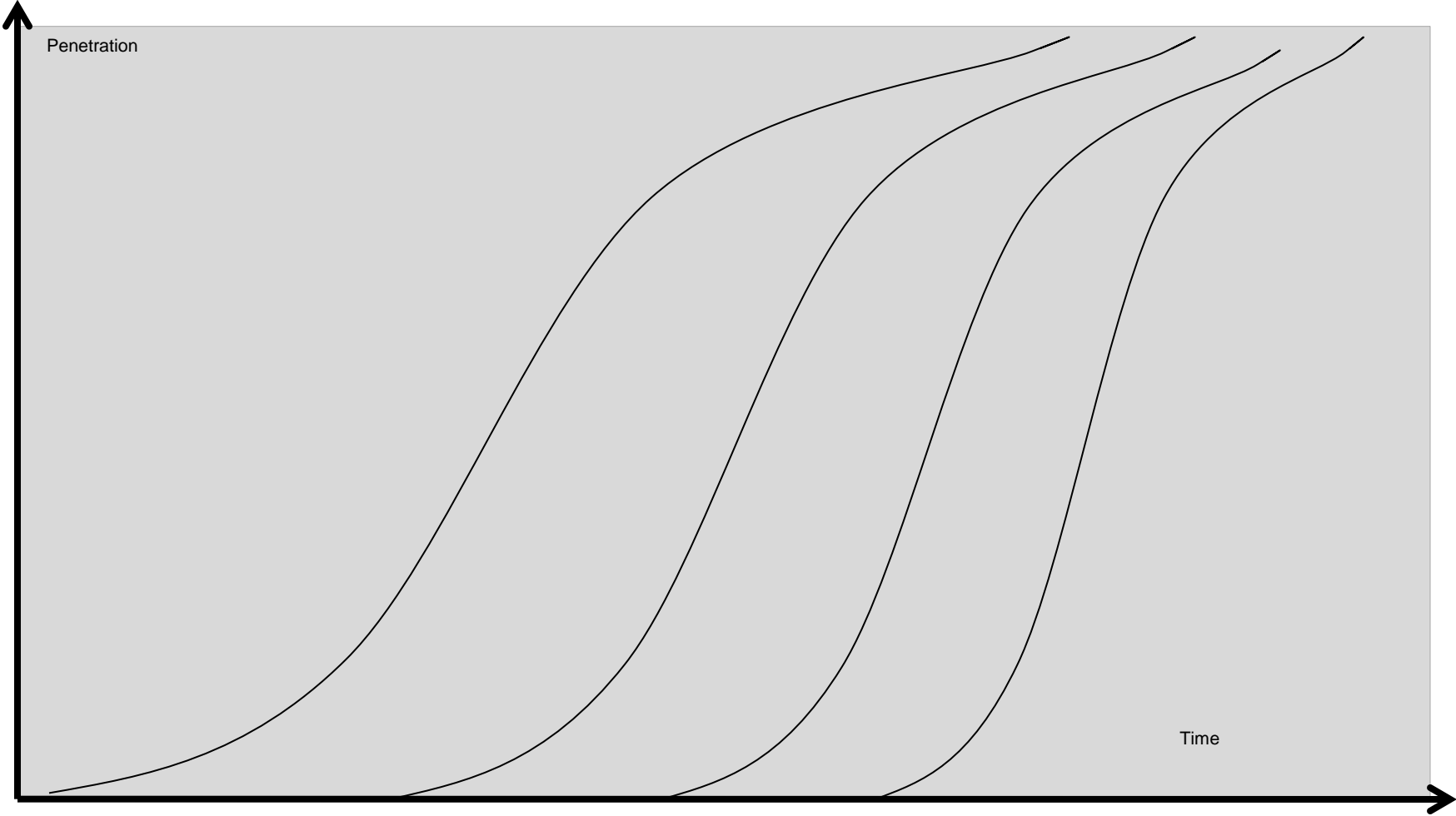
Further, most expensive biologics rapidly cross the maximum cost bore by PDP; lack of incentive to manage these products

Survey: payors' reasons for struggling to control use of marginal product when cheap alternative is available



Source: Bernstein survey of US Payors asking managed care formulary decision makers why marginally better second generation drugs retain scripts even after generics are available for the first generation drug; scale 1-5, black represents 4-5 score, green – 1 score

Summary: we expect gradually improving adoption as barriers are removed; regulators have room to play in proactively addressing some barriers



Source: Bernstein

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Text of payor survey question (I)

Branded pharmaceutical companies implement a variety of life-cycle management tools to reduce the impact of generic entries on aging products. The strategy is to replace the drug that is going generic with a new drug that may have only minor improvements but much longer patent life. Some of the newer drugs have only minor benefit but cost significantly more than the generic. We would have thought that use would shift to the cheaper generic once it becomes available. To this point we have not seen this happen in a material way.

Some examples of these situations are:

- New enantiomer: Cephalon sold wakefulness drug Provigil, a racemic mixture of a modafinil. To extend the life of the franchise, Cephalon launched Nuvigil, a single enantiomer of Provigil. When Provigil went generic, Nuvigil prescriptions trend flattened but did not drop.
- Dosage amount: Medicis knew that three dosages of Solodyn (an acne medicine) would go generic. They created 5 new dosages ahead of the generic event - AND - pulled the old dosages off the market. When the generic event came, the generics only gained 3% of TRx.

We hypothesized on the reasons for the lack of 'switch back' and came out with several non-mutually exclusive ideas. We would like to ask your view on these ideas. To emphasize, we are looking for reasons why marginally beneficial oral/retail drugs are used. We are not asking here about the value proposition of novel, expensive drugs.

In the next eight questions we will ask you to evaluate the putative reasons why managed care did not drive a switch back in these drugs.

Please rate the statement below on a scale of 1 to 5, with:

- (1) - Totally off base
- (2) - Unlikely to be a reason, perhaps in rare occasions
- (3) - On occasion could be the reason
- (4) - An important reason
- (5) - The most important reason

Source: Bernstein

Text of payor survey question (II)

- 1. Drugs are worth it.** There is real differentiation between the original and second generation drugs we mention above. Payors believe they are 'worth' having available to patients
- 2. Branded pharmaceuticals are effective in finding solution.** There is an effort by the managed care community to limit use of marginally beneficial drugs. However, pharmaceutical companies are very effective in convincing physicians to use them, getting around plan barriers by rebating patient's copays etc.
- 3. The relationship between payors and drug companies is more cooperative.** Drug companies spend significant dollars in rebates so PBM/Health plans need to work with them' across a portfolio of drugs; blocking marginal drugs completely would disrupt the relationship and ultimately does not make economic sense.
- 4. The managed care industry has not gotten to it yet.** Second generation mid-size drug spend is a small proportion of a health plans budget; it could be managed, but it is not a high priority.
- 5. The employers/employees are not ready.** PBM/Health plans are hired to administer plans but it is the employer/eventual payor who make the final decision. Most employers are not motivated enough to push for lower drug spend costs (very few have closed formularies and often reject step edits/prior authorizations).
- 6. Physician resistance.** Doctors largely resist therapeutic switches. The cost of contacting a physician to convince them to write a 1st gen product is too much for a typical retail, non-biologic drug, making it 'not worth it'.
- 7. The infrastructure is not there.** PBM/Health plans would like to be able to switch patients back to the generic but lack the tools to effectively do this in a systemic way.
- 8. An agency problem.** It can be done, but it is against the PBM/Health plans economic interest to significantly reduce the total cost of drugs acquisition.

Source: Bernstein

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