CAMBIO DEL CONTEXTO DE LA INDUSTRIA BIOTECNOLOGICA MUNDIAL: RETOS PARA EL DESARROLLO DE PRODUCTOS Y NEGOCIOS.

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Taller OMPI, 6 de Febrero de 2019

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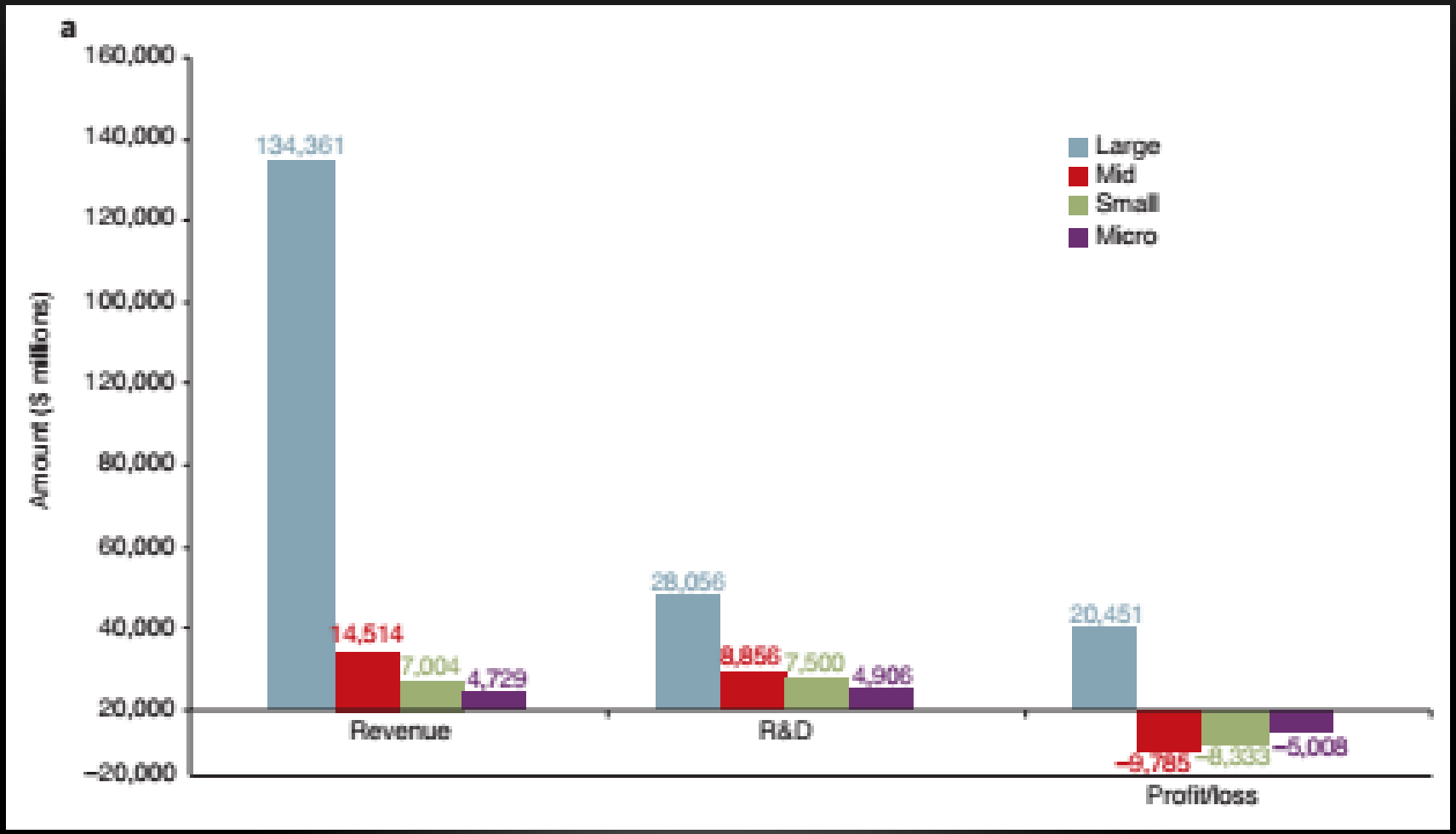
1. LA CONCENTRACION DE LA GANANCIA.

Table 3 The 20 top-selling biopharmaceutical products in 2017

Rank	Product	Sales, 2017 ($ billions)[a]	Cumulative sales, 2014–2017 ($ billions)	Year first approved	Company	Patent expiry[b]	Biosimilar version(s) approved
1	Humira (adalimumab; anti-TNF)	18.94	62.6	2002	AbbVie, Eisai	2016 (US) 2018 (EU)	Halimatoz/Hefiya/Hyrimoz, Amgevita/Amjevita/Solymbic, Cyltezo, Imraldi
2	Enbrel (etanercept; anti-TNF)	8.34	35.4	1998	Amgen, Pfizer, Takeda Pharmaceuticals	2015 (EU) 2028 (US)	Erelzi, Benepali
3	Rituxan/MabThera (rituximab; anti-CD20)	7.78	29.1	1997	Roche, Biogen Idec	2013 (EU) 2016 (US)	Blitzima/Truxima, Ritemvia, Rituzena, Rixathon/Riximyo
4	Remicade (infliximab; anti-TNF)	7.77	35.6	1998	Johnson & Johnson, Merck, Mitsubishi Tanabe Pharma	2015 (EU) 2018 (US)	Zessly, Ixifi, Renflexis/Flixabi, Inflectra/Remsima
5	Herceptin (trastuzumab; anti-HER2)	7.39	27.1	1998	Roche	2014 (EU) 2019 (US)	Herzuma, Kanjinti, Trazimera, Ogivri, Ontruzant
6	Avastin (bevacizumab; anti-VEGF)	7.04	27.0	2004	Roche	2017 (US) 2019 (EU)	Mvasi
7	Lantus (insulin glargine)	6.72	27.4	2000	Sanofi	2014 (EU & US)	Semglee, Lusduna, Abasaglar/Basaglar
8	Eylea (aflibercept; anti-VEGF)	5.93	18.0	2011	Regeneron, Bayer	2020 (EU) 2021 (US)	
9	Opdivo (nivolumab; anti-PD-1 receptor)	5.79	11.4	2014	Bristol-Myers Squibb, Ono Pharmaceutical	2027 (US) 2026 (EU)	
10	Neulasta (pegfilgrastim)	4.53	20.1	2002	Amgen, Kyowa Hakko Kirin	2014 (US) 2015 (EU)	Fulphila
11	Stelara (ustekinumab; anti-IL-12 & IL-23)	4.01	12.2	2009	Janssen Cilag (Johnson & Johnson)	2023 (US) 2024 (EU)	
12	Keytruda (pembrolizumab, anti-PD-1)	3.81	5.7	2014	Merck	2036 (US) 2028 (EU)	
13	Prolia/Xgeva (denosumab, anti-RANKL)	3.54	11.6	2010	Amgen	2025 (US) 2022 (EU)	
14	Lucentis (ranibizumab; anti-VEGF)	3.38	14.3	2006	Roche, Novartis	2016 (EU & US)	
15	Novolog/Novorapid (insulin aspart)	3.31	11.7	1999	Novo Nordisk	2015 (EU & US)	
16	Soliris (eculizumab; anti–C5 complement protein)	3.14	10.7	2007	Alexion Pharmaceuticals	2021 (US) 2020 (EU)	
17	Simponi (golimumab; anti-TNF)	2.94	9.7	2009	Merck, Janssen, Mitsubishi Tanabe	2024 (EU & US)	
18	Humalog mix 50-50 (insulin lispro)	2.86	11.3	1996	Eli Lilly	2014 (US) 2015 (EU)	Insulin lispro Sanofi
19	Xolair (omalizumab) anti-IgE	2.75	8.7	2003	Roche, Novartis	2017 (EU & US)	
20	Aranesp/Nesp (darbepoetin alfa)	2.62	10	2001	Amgen, Kyowa Hakko Kirin	2016 (EU) 2024 (US)	

[a]Financial data from La Merie Business intelligence. [b]Patent data from various sources, including http://www.gabionline.net/Biosimilars/General/Biologicals-patent-expiries.
HER2, human epidermal growth factor receptor 2; IgE, immunoglobulin E; IL, interleukin; PD-1, programmed cell death receptor 1; RANKL, receptor activator of nuclear factor-κB ligand; VEGF, vascular endothelial growth factor.


a
160,000
140,000
120,000
100,000
120,000
80,000
60,000
40,000
20,000
−20,000
Amount ($ millions)
134,361
14,514
7,004
4,729
28,056
9,856
7,500
4,906
20,451
−9,785
−8,333
−5,009
Revenue
R&D
Profit/loss
Large
Mid
Small
Micro

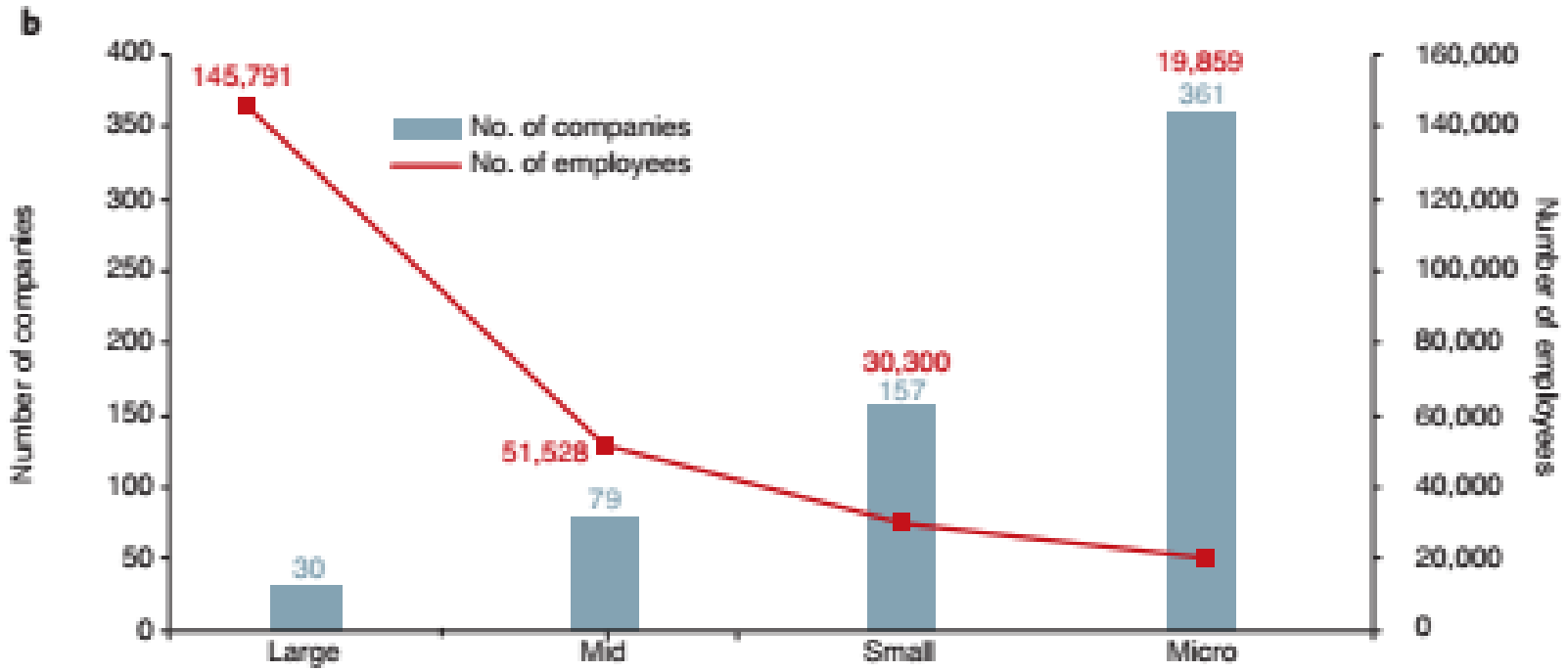


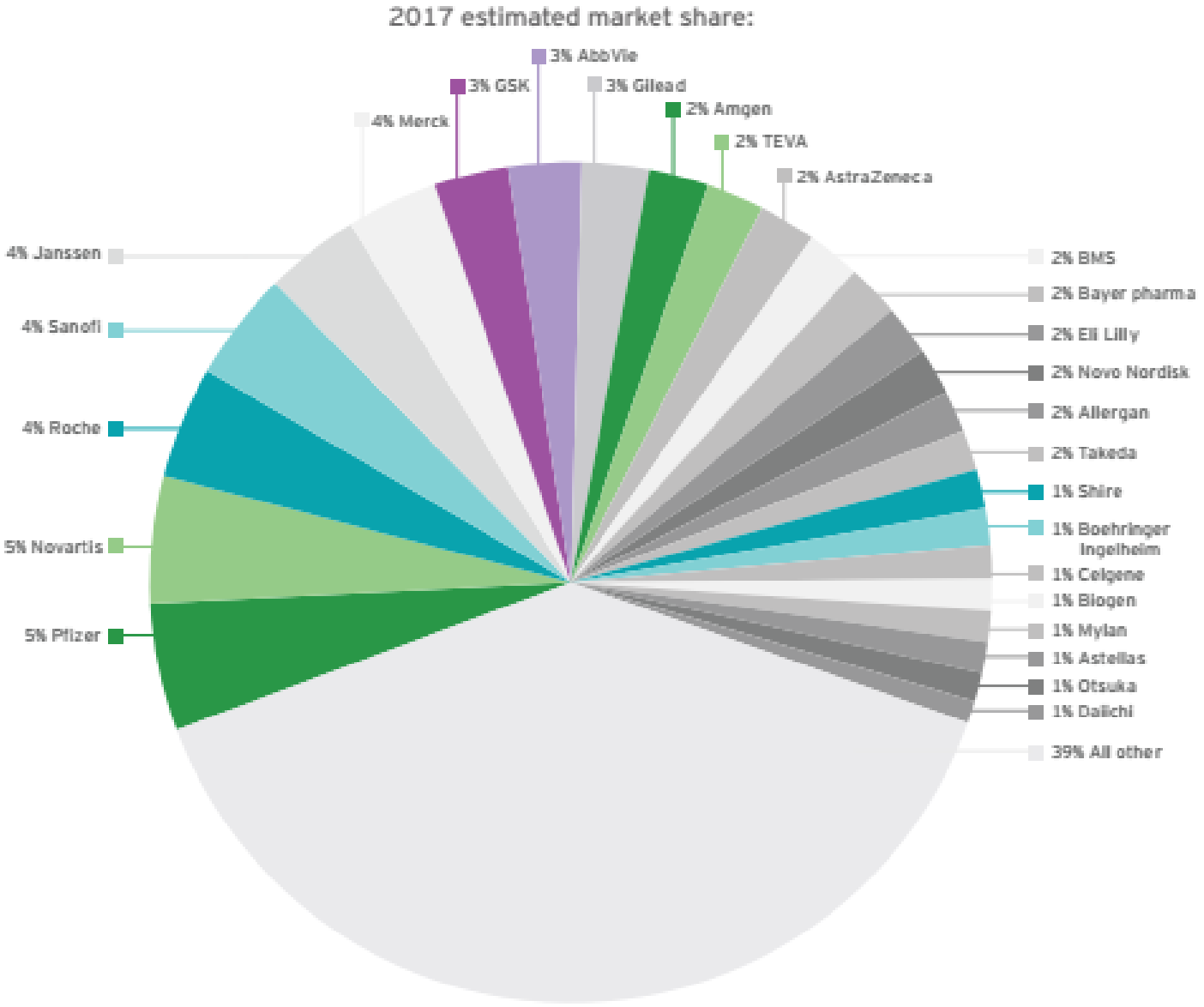
Figure 2 Public biotech barometers. (a) Public biotech company revenue, R&D spending, net profit and loss. (b) Number of companies and employees by market cap. Large cap, ≥$5 billion; mid-cap, $1 billion to < $5 billion; small cap, $250 million to < $1 billion; micro-cap, <$250 million.

EY survival index, 2015–16

	US		Europe	
	2016	2015	2016	2015
More than 5 years of cash	22%	25%	29%	30%
3-5 years of cash	13%	13%	10%	16%
2-3 years of cash	11%	16%	13%	12%
1-2 years of cash	25%	23%	25%	19%
Less than 1 year of cash	30%	22%	22%	22%

Source: EY, Capital IQ and company financial statement data.

Exhibit 5. Global pharmaceutical industry remains highly fragmented: no leaders have greater than 5% share of US$1 trillion global market



Source: IMS, S&P Capital IQ and EY analysis.

2. **EL ALTO COSTO DEL DESARROLLO.**

UN REPORT 2016: PROMOTING INNOVATION AND ACCESS TO HEALTH TECHNOLOGIES

R&D costs – a wide range of estimates

[1] PWC (2012) From vision to decision: Pharma 2020. Available at: http://www.pwc.com/gx/en/pharma-life-sciences/pharma2020/assets/pwc-pharma-success-strategies.pdf

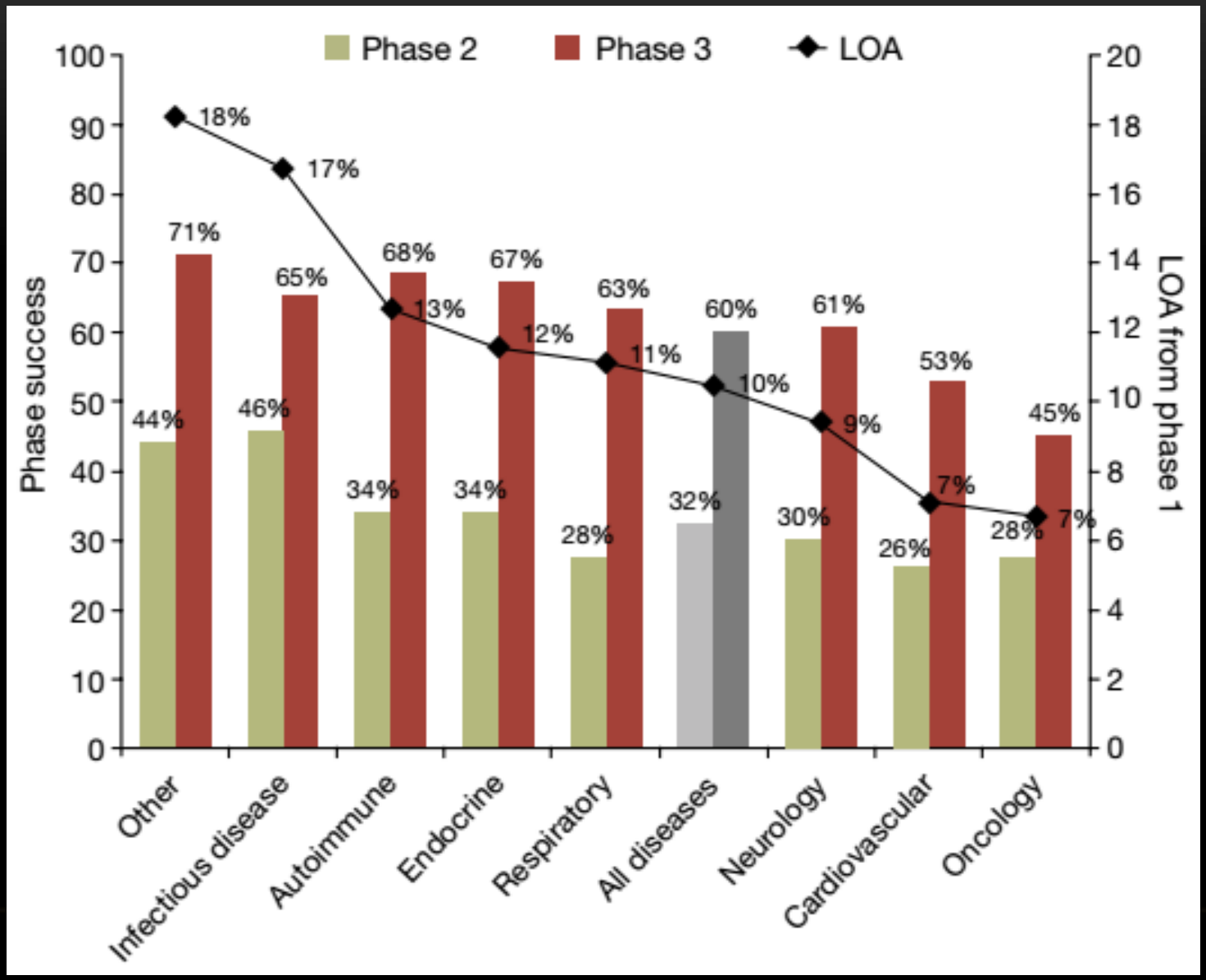
[2] DiMasi, J.A., *et al.* 2016 Innovation in the pharmaceutical industry: New estimates of R&D costs. *Journal of Health Economics* 22 (2003): 151 – 185. Available at: http://fds.duke.edu/db?attachment-25--1301-view-168

[3] PhRMA (2015) Profile bio pharmaceutical research industry. Available at: http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf

[4] Light, W & Warburton, R. (2011) Demythologizing the high costs of pharmaceutical research. *BioSocieties*. Available at: http://www.pharmamyths.net/files/Biosocieties_2011_Myths_of_High_Drug_Research_Costs.pdf

[5] DNDi (2014) An innovative approach to R&D for neglected patients: Ten years of experience and lessons learnt by DNDi. Available at http://www.dndi.org/images/stories/pdf_aboutDNDi/DNDiModel/DNDi_Modelpaper_2013.pdf

PHASE SUCCESS RATES FOR BIOTECH DRUGS BY INDICATIONS



3. LA ESCALADA DE PRECIOS.

ANTICANCER DRUGS PRICING IS GROWING STEADILY

- **The global anticancer drug market, which currently exceeds US$ 100 Billion per annum, is expected to grow to $ 150 billion by 2020.**

- **In the USA, the average price of an anticancer drug routinely exceeds US$ 100,000 per year or course of treatment.**

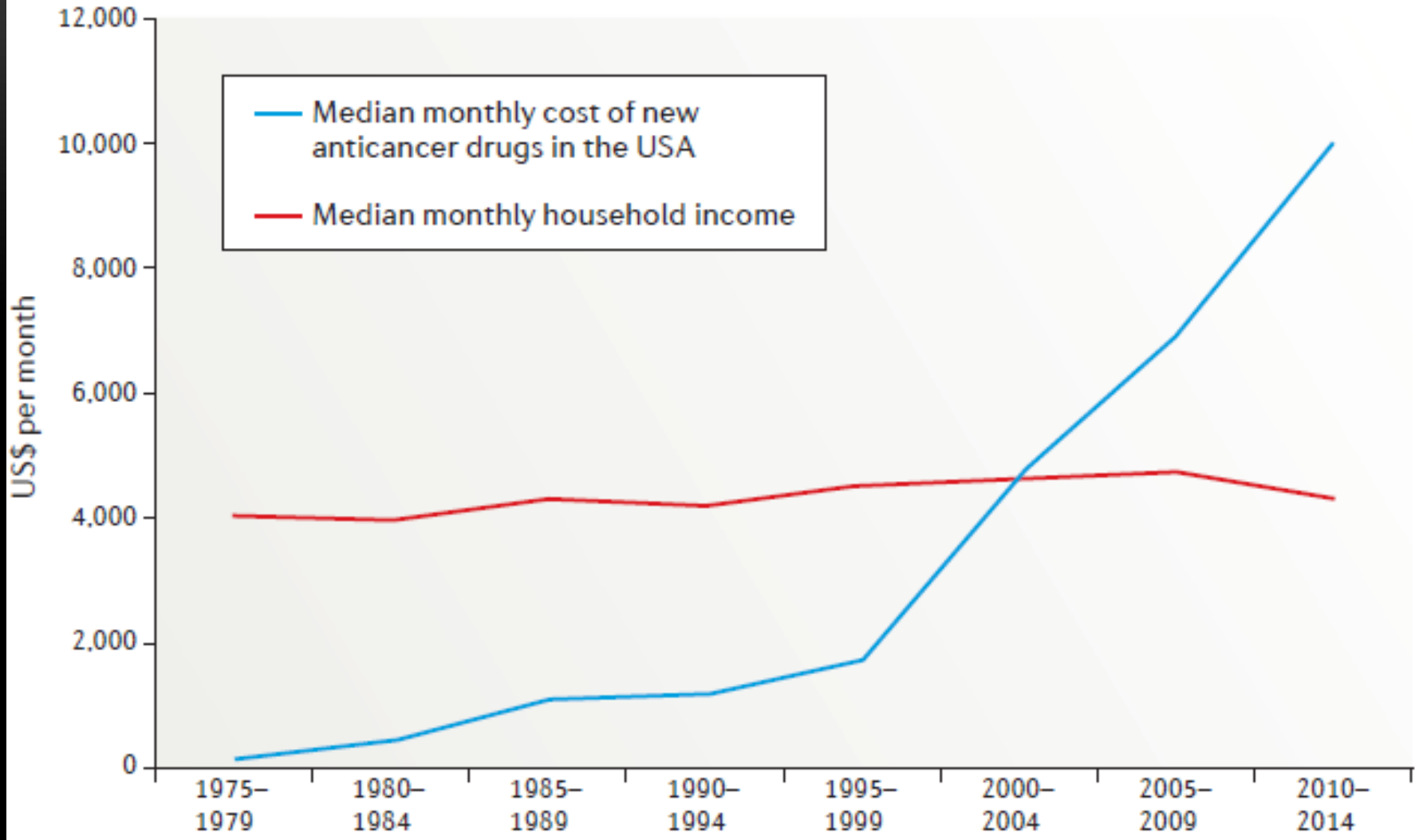


Figure 2 | **Median monthly launch price of a new anticancer drug, compared with median monthly household income from 1975–2014 in the USA.** Data on household incomes were obtained from the 2015 United States Census[130], and drug prices were obtained from Bach & Schnorr[131].

HIGH ONCOLOGY DRUG PRICES DO HARM PATIENTS AND SOCIETIES

- In the USA, patients with cancer who require treatment that incurs a high level of medical expense might be forced to declare personal bankruptcy.
- Thus, a diagnosis of cancer is associated with a 2.65 times increased risk of going bankrupt.
- No national health system anywhere in the world can afford to make all new anticancer drugs available to patients.

Nat Rev Clin Oncol. 2017 Jun;14(6):381-390.

4. EL BENEFICIO MARGINAL DE LAS TERAPIAS ONCOLOGICAS.

ANTICANCER DRUGS APPROVED DURING LAST 15 YEARS SHOW MARGINAL (LOW-VALUE) BENEFITS ON REAL WORLD POPULATION.

- The median improvements in PFS and OS with 71 consecutive therapies approved by the FDA for metastatic cancer between 2002 and 2014 were 2.5 months and 2.1 months, respectively.

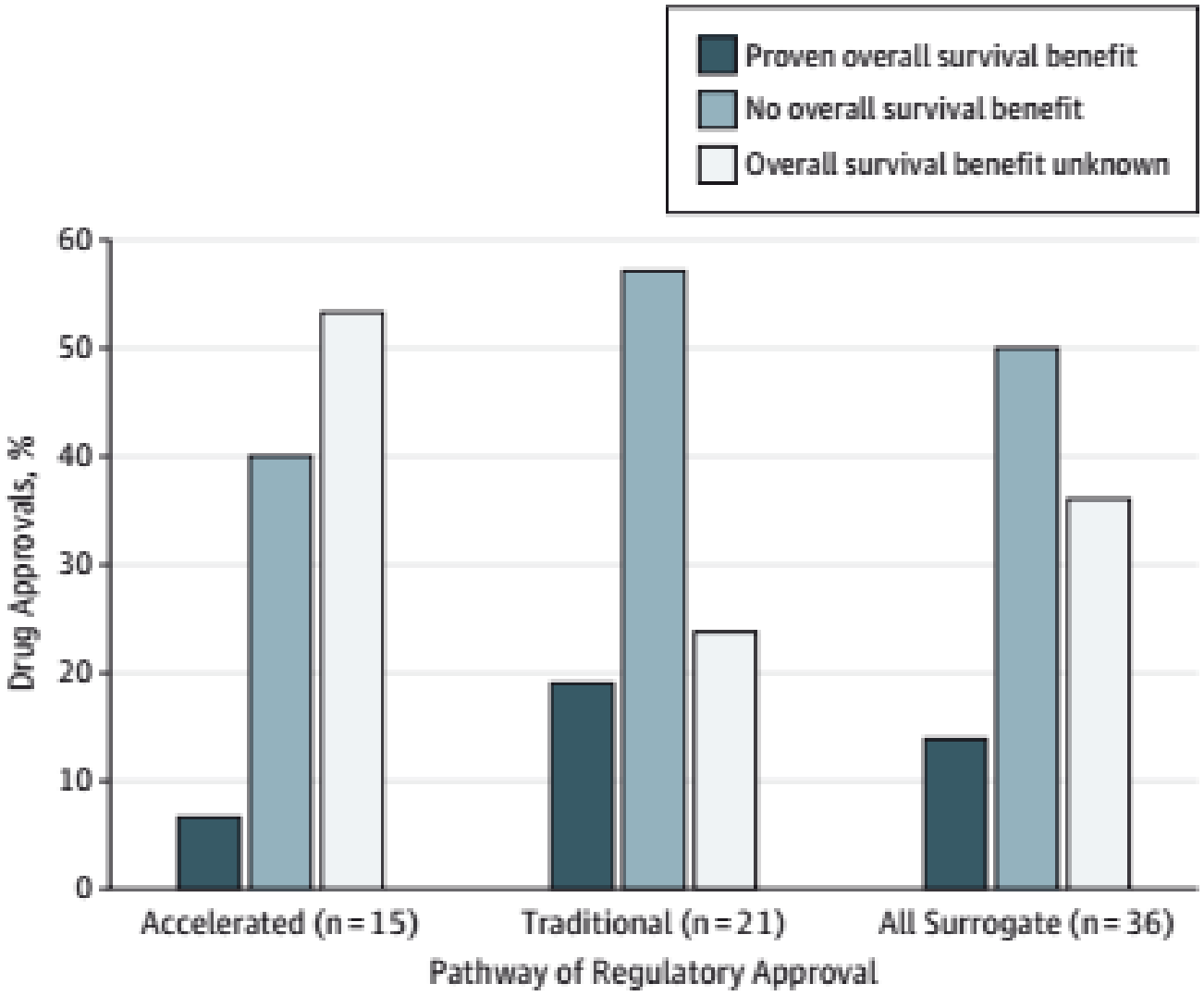
  JAMA Otolaryngol. Head Neck Surg. **140**, 1225–1236 (2014).

- In another analysis, of 47 pharmaceuticals approved by the US FDA in 2014–2016, only 9 (19%) met the significant clinical benefit standard with regard to OS stablished by ASCO.

  Ann Oncol. 2017:28(1):157–62

- “We must accept that the concept of building on incremental gains by combining marginally effective regimens has not brought the substantive progress for patients with cancer that we need to achieve”.

Figure 2. Overall Survival Results for Cancer Drug Approvals Granted on the Basis of a Surrogate End Point



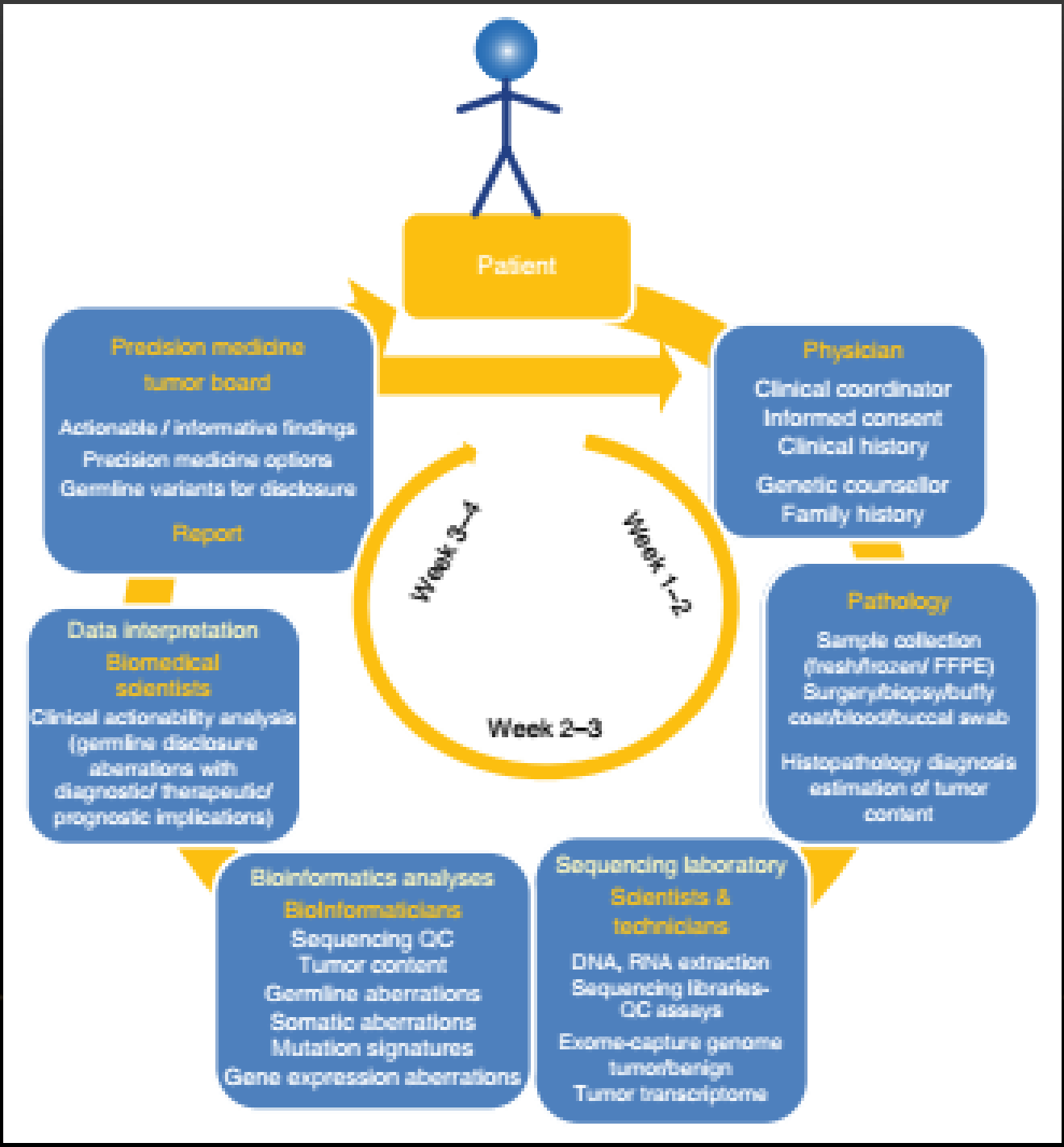
It includes all cancer drugs approved from January 1, 2008, through December 31, 2012.

54 drugs were identified, with 36 drugs (67%) approved on the basis of a surrogate end point.

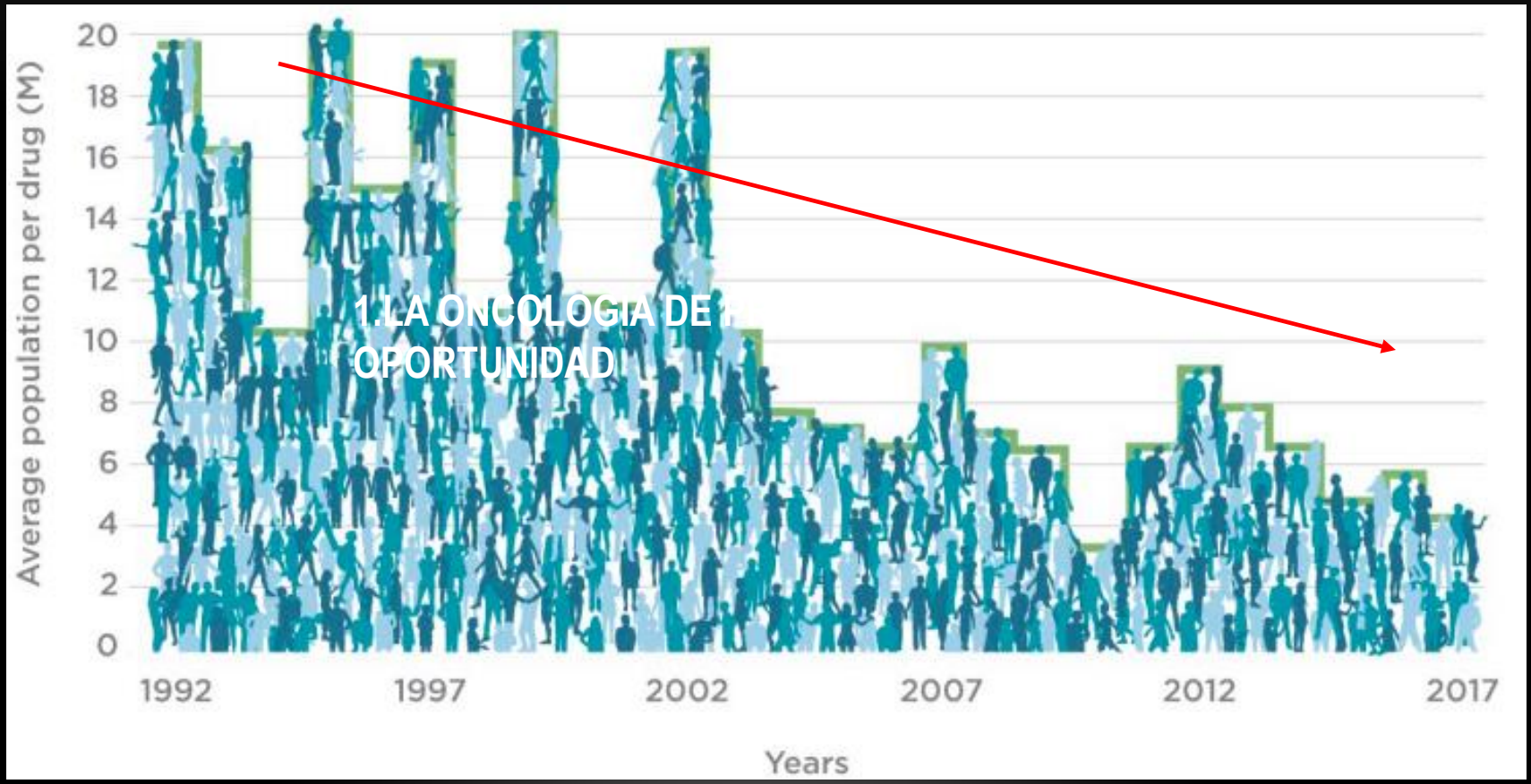
OS outcomes were assessed with a median follow-up of 4.4 years.

JAMA Internal Medicine Published online October 19, 2015

5. LA ONCOLOGIA DE PRECISION: RETO


Patient
Physician
Clinical coordinator
Informed consent
Clinical history
Genetic counsellor
Family history
Pathology
Sample collection
(fresh/frozen/ FFPE)
Surgery/biopsy/butty
coat/blood/buccal swab
Histopathology diagnosis
estimation of tumor
content
Sequencing laboratory
Scientists &
technicians
DNA, RNA extraction
Sequencing libraries-
QC assays
Exome-capture genome
tumor/benign
Tumor transcriptome
Bioinformatics analyses
Bioinformaticians
Sequencing QC
Tumor content
Germline aberrations
Somatic aberrations
Mutation signatures
Gene expression aberrations
Data interpretation
Biomedical
scientists
Clinical actionability analysis
(germline disclosure
aberrations with
diagnostic/ therapeutic/
prognostic implications)
Precision medicine
tumor board
Actionable / informative findings
Precision medicine options
Germline variants for disclosure
Report
Week 3–4
Week 1–2
Week 2–3

PO challenge: Deepening the drop in average target population size for new drugs approved by FDA over the last 25 years.



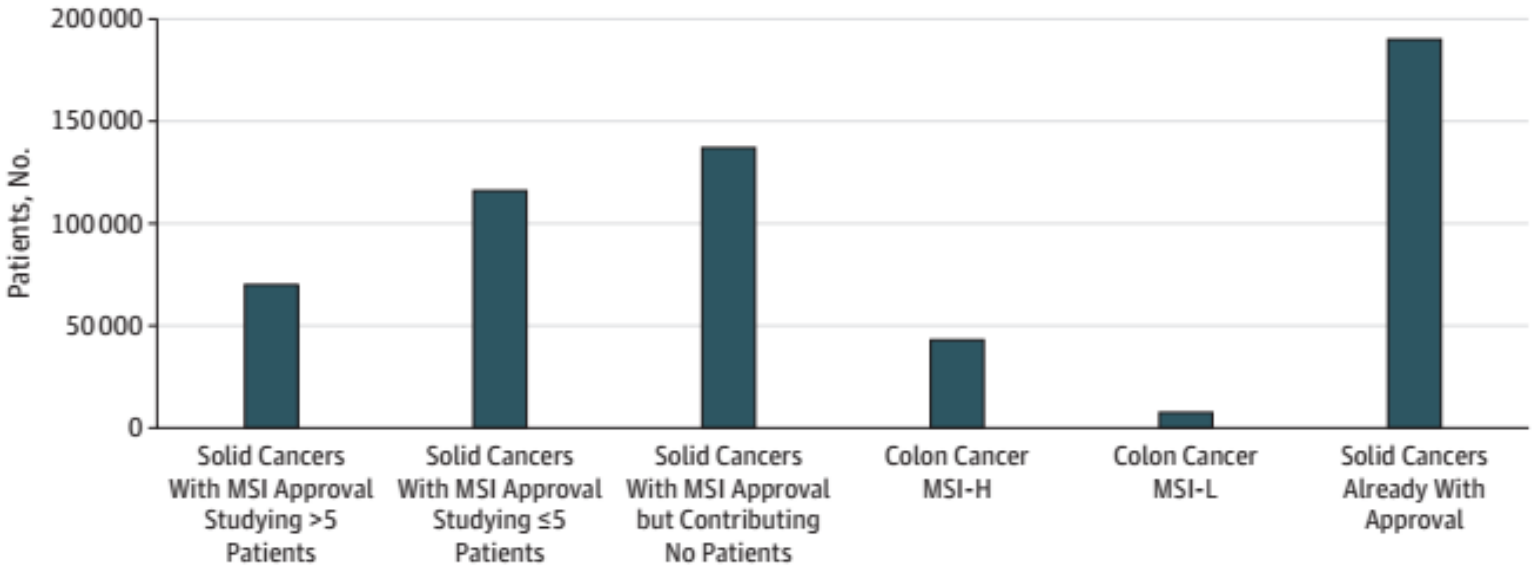
Biocentury,Sep-2018

5. LA ONCOLOGIA DE PRECISION: OPORTUNIDAD

PO OPORTUNITY: KEYTRUDA AS A LANDMARK CASE STUDY

- Keytruda (pembrolizumab) received accelerated approval on May 2017 for patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors that have progressed on prior therapy.
- It was the 1st drug authorized for use based on a molecular biomarker rather than a traditional histopathologic diagnosis **(1st tissue-agnostic approval).**
- The approval was based on 59 ptes treated in a series of uncontrolled phase II trials, demonstrating a 46% objective response rate.
- Among these 59 ptes , 14 cancers were represented. Only two of them had more than 10 ptes in the sample.

Figure. The US FDA's Approval of Pembrolizumab in All Solid Tumors With MSI-H or dMMR



JAMA Oncology Published online December 28, 2017

6. BIOFARMA 3.0: MODELO DE NEGOCIOS EMERGENTE

BioPharma 1.0

- **Blockbuster model** (drugs selling over a billion USD / year).
- Broad indications for large target populations.
- Market Access through intensive market expenses.

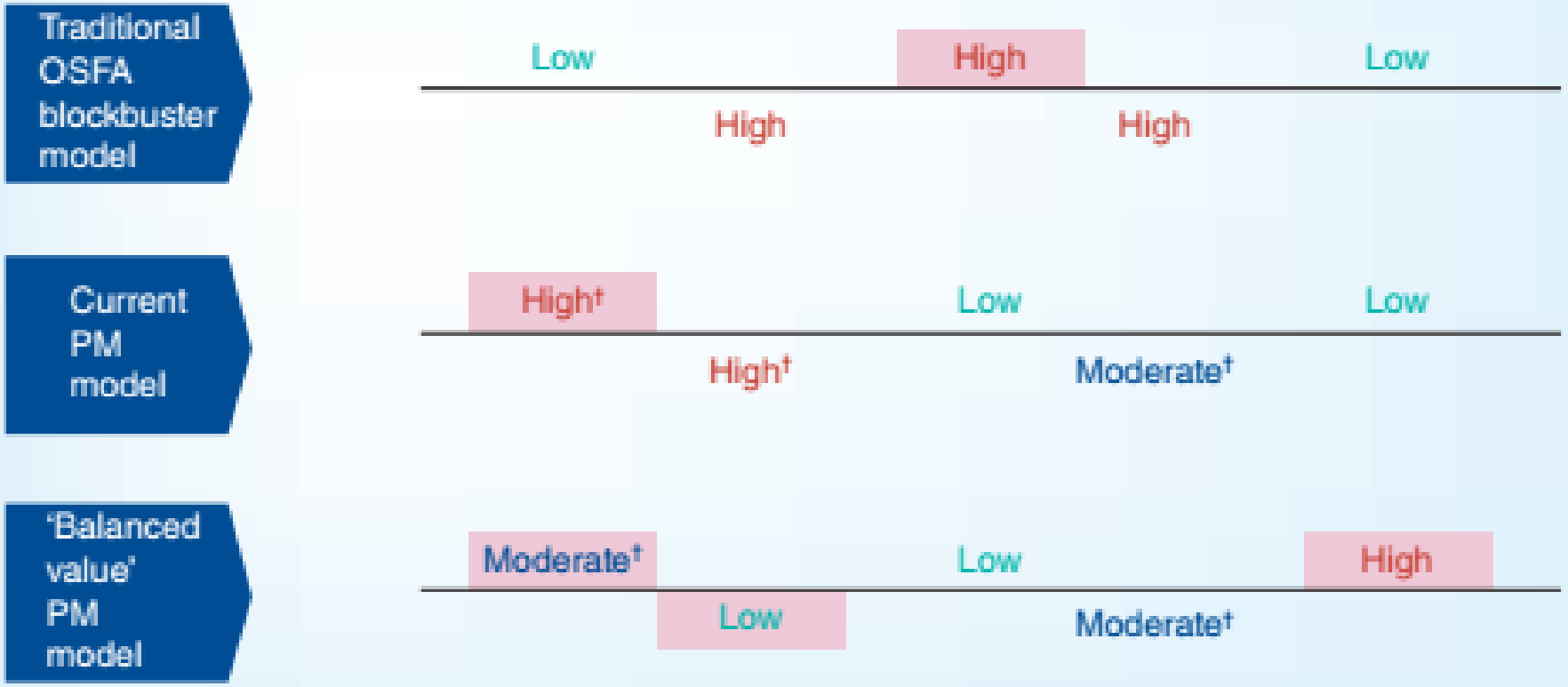
BioPharma 2.0

- Hanging fruit targets were already harvested.
- Patent cliffs created robust generic market.
- Blockbuster replaced by the specialty model (targeting **rare disease with high priced drugs**).
- Market Access through smaller, targeted sale forces.

BioPharma 3.0

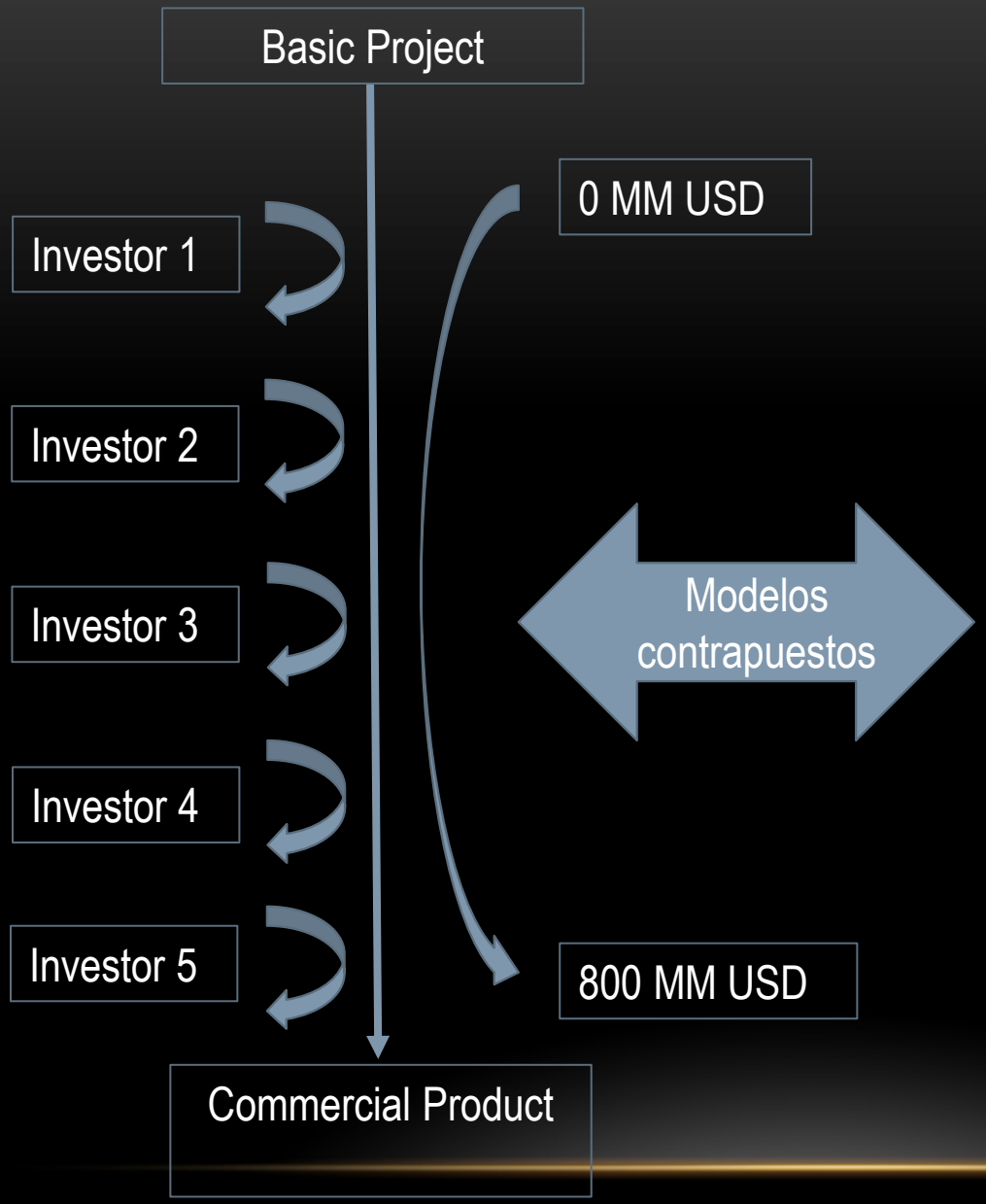
- "Best in class" is about cost-effectiveness.
- Increasing pressure to end patent extension schemes.
- Therapeutic solutions + companion diagnostics.
- Real World Evidence combined with new biological and data tools to add value through the entire life cycle of treatment.
- Data assisted risk management programs for reducing failure rate in clinical trials.

$$\text{Rx product ROI} = \frac{\text{(Price per Rx product unit} \times \text{Rx product units sold per year} \times \text{years of sales)}}{\text{(Cost of development + cost of commercialization)}}$$



= critical lever to ensure Rx product profit

6.a COMO VENCER EL VALLE DE LA MUERTE?



Modelo de licencia y codesarrollo:

- Complejo de manejar cuando el licenciante es una empresa grande con un amplio pipeline.
- Falta de foco del equipo de dirección desalienta a los licenciatarios.
- Poca transparencia en la asignación de financiamiento por proyectos y en las prioridades de la toma de decisiones.

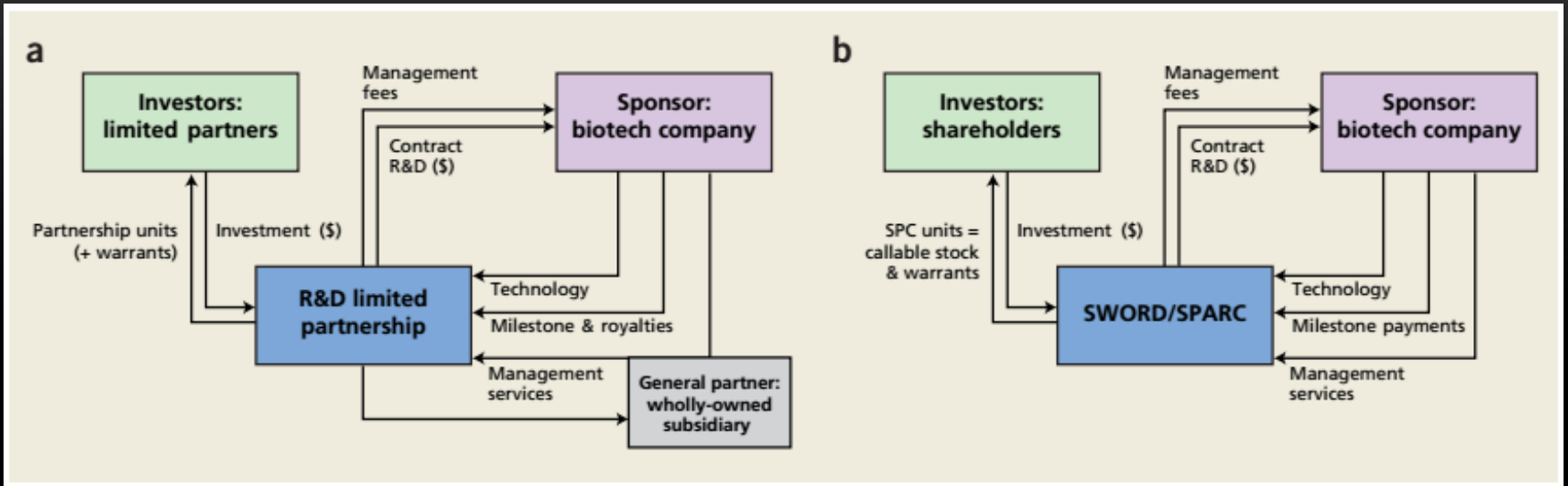


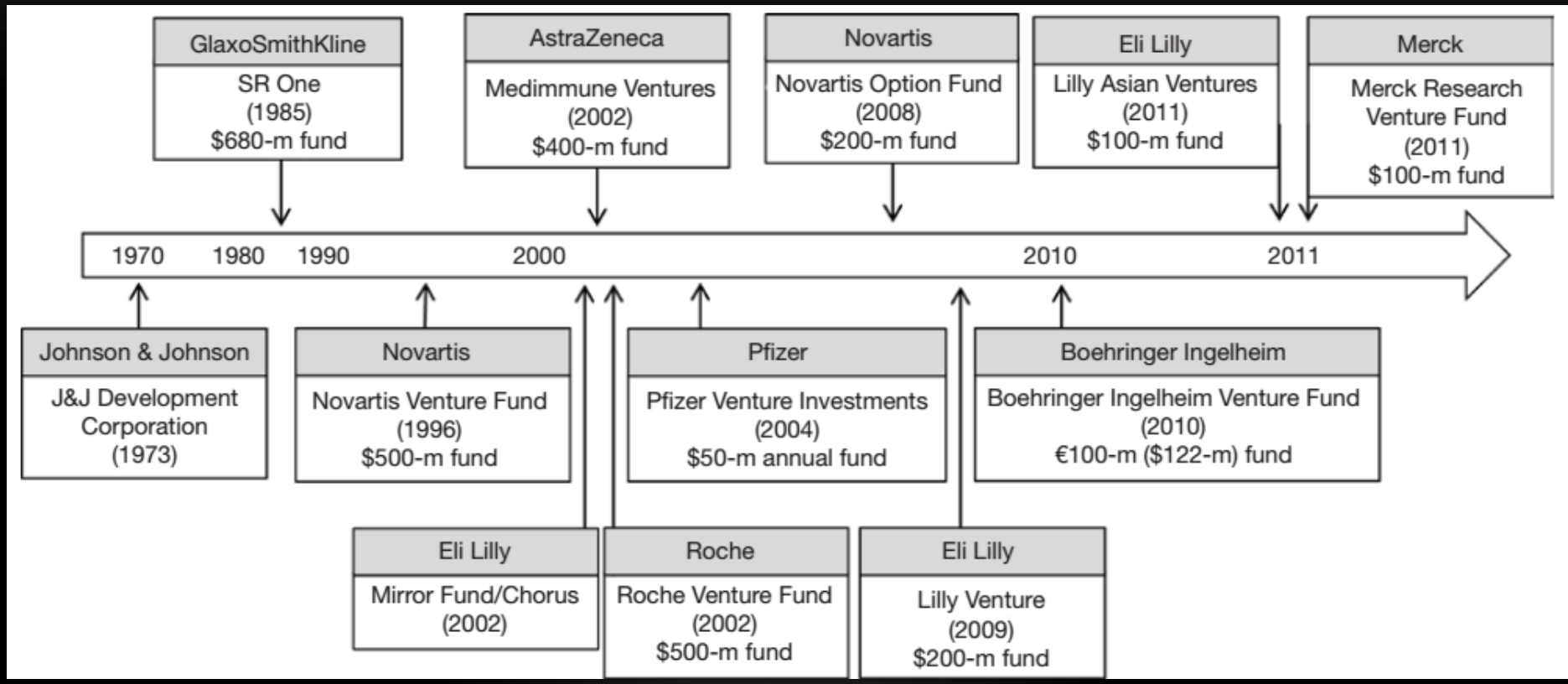
Figure 1 SPE structure. (**a**) Structure of R&D limited partnerships. (**b**) Structure of special purpose corporations.

- La Biotech pone sus activos de PI en una SPV con capacidad legal propia, estados financieros independientes y equipo de dirección dedicado.
- Cede participación a los inversionistas, que aportan financiamiento, pero mantienen control efectivo sobre las operaciones de la SPV.
- La Biotech ofrece garant{ias al Inversionista en caso de fracaso y ejerce opción de recompra en caso de éxito, en cuyo caso recupera control total sobre los activos. (Ej: Amgen con Filgrastim)

Table 1 Listing of all known SPEs

SPE	Sponsoring company	Nature of SPE	Offer year	SPE money raised ($ millions)
Genentech Clinical Partners, LP	Genentech	R&D LP	1982	$55.6
R&D LP	Scios (Cal. Biotech)	R&D LP	1982	$27.5
Cetus Healthcare, LP	Cetus	R&D LP	1983	$75.0
Genentech Clinical Partners II, LP	Genentech	R&D LP	1983	$34.0
Biogen Medical Products, LP	Biogen	R&D LP	1984	$30.0
Centocor Oncogene Research Partners, LP	Centocor	R&D LP	1984	$5.0
Centocor Cardiovascular Imaging Partners, LP	Centocor	R&D LP	1985	$23.2
Genentech Clinical Partners III, LP	Genentech	R&D LP	1985	$33.2
Centocor Partners II, LP	Centocor	R&D LP	1986	$54.3
Cetus Healthcare, LP II	Cetus	R&D LP	1986	$62.0
Chiron Ophthalmic Research Partners	Chiron	R&D LP	1986	NA
Amgen Clinical Partners, LP	Amgen	R&D LP	1987	$83.6
Centocor Partners III, LP	Centocor	R&D LP	1987	$52.8
Genzyme Clinical Partners, LP	Genzyme	R&D LP	1987	$10.0
Tocor	Centocor	SPC	1989	$31.0
Genentech Clinical Partners IV, LP	Genentech	R&D LP	1989	$72.5
Genzyme Development Partners, LP	Genzyme	R&D LP	1989	$36.7
Receptech	Immunex	SPC	1989	$27.0
Neozyme	Genzyme	SPC	1990	$47.3
SciGenics	Genetics Institute	SPC	1991	$42.0
Aramed	Sicor (Gensia)	SPC	1991	$53.0
Gensia Clinical Partners	Sicor (Gensia)	R&D LP	1991	$26.3
Alkermes Clinical Partners, LP	Alkermes	R&D LP	1992	$46.0
Tocor II	Centocor	SPC	1992	$90.0
Cephalon Clinical Partners, LP	Cephalon	R&D LP	1992	$40.0
CytoRad	Cytogen	SPC	1992	$35.0
Neozyme II	Genzyme	SPC	1992	$85.0
Dura Delivery Systems, Inc.	Dura Pharm.	SPC	1993	$13.0
Spiros Development Corp.	Dura Pharm.	SPC	1995	$28.0
ALRT (Allergan Ligand Retinoid Therapeutics)	Ligand (Allergan)	SPC	1995	$33.0
Spiros Development Corp. II	Dura Pharm.	SPC	1997	$94.0
ICOS Clinical Partners, LP	ICOS	R&D LP	1997	$79.8
	Total	32		$1,426
	Average			$46.0
	Standard deviation			$24.2

Las Big Farma han creado sus propios fondos de capital para invertir en activos externos.



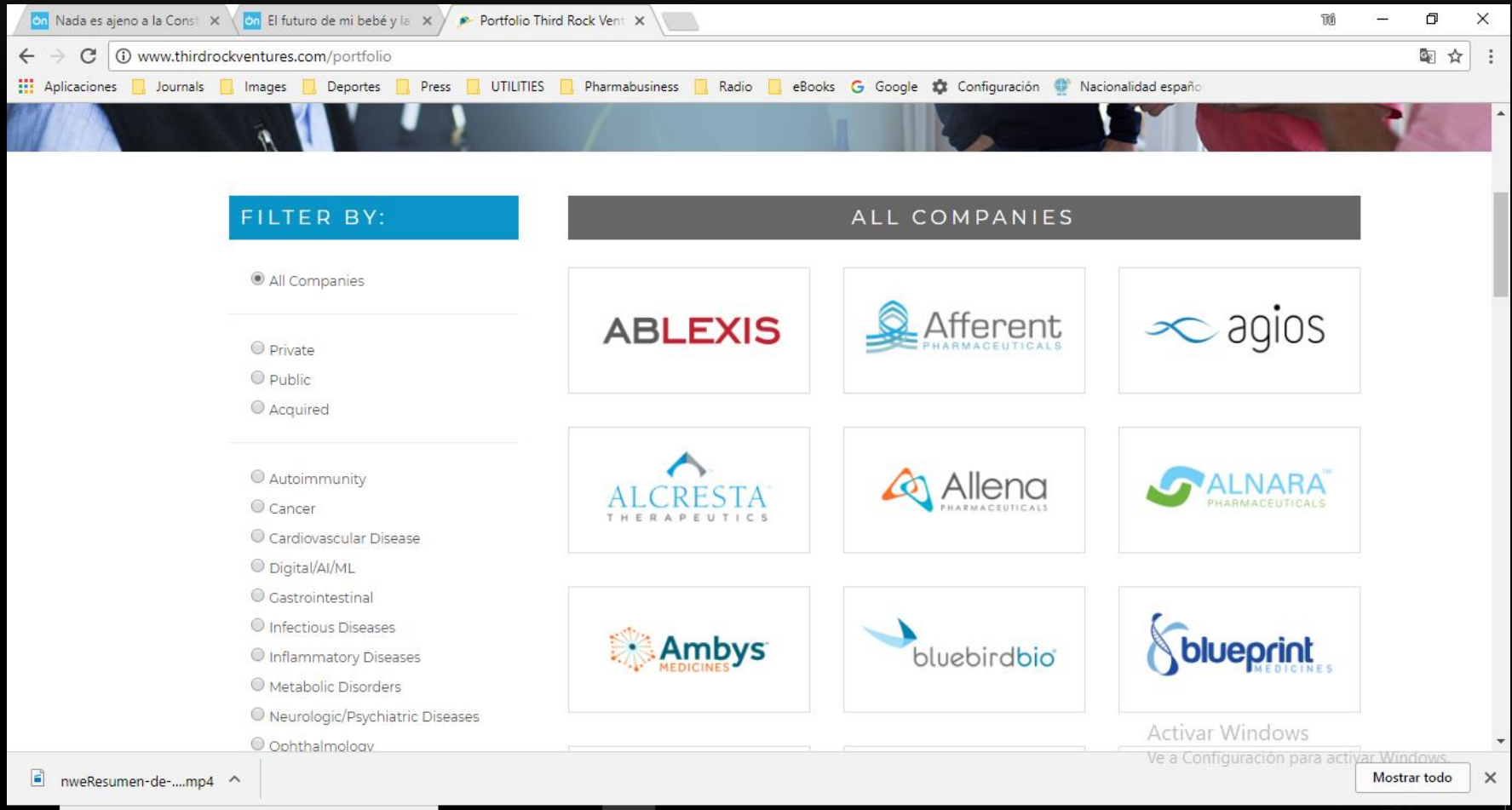
NATURE BIOTECHNOLOGY VOLUME 32 NUMBER 10 OCTOBER 2014

Table 4 Most active investors in leading series A rounds, 2008–2017

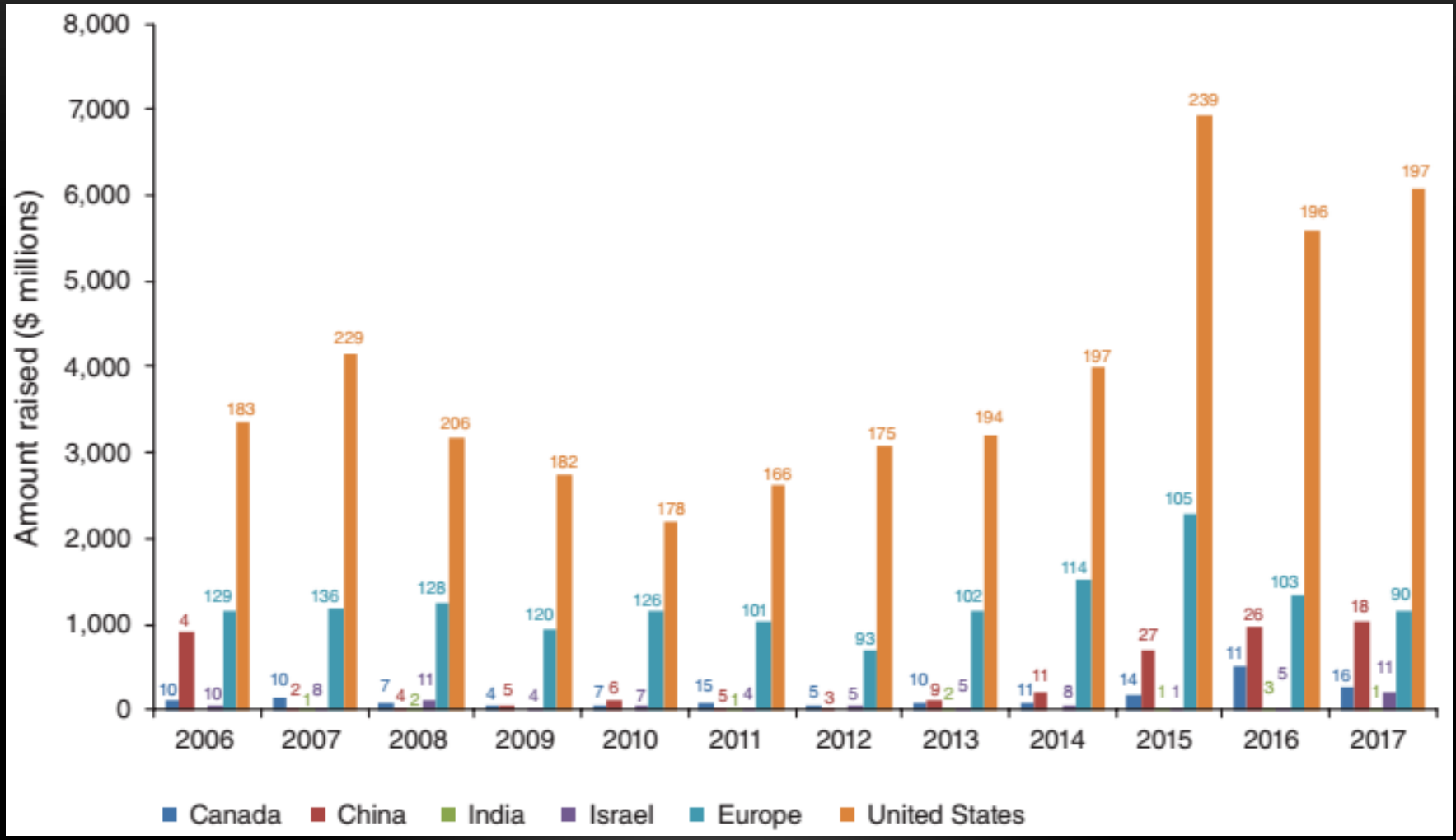
Investor	Number of financings	Total amount raised ($)
Atlas Venture	26	548,465,450
Third Rock Ventures	24	998,800,000
Arch Venture Partners	19	763,380,455
OrbiMed Advisors	18	508,250,000
MPM Capital	18	477,613,910
Sofinnova Partners	16	325,328,436
Novartis	15	344,742,670
Versant Ventures	15	385,135,850
5AM Ventures	15	399,200,000
New Enterprise Associates	14	400,300,000
Novo Holdings	14	244,499,290
Frazier Healthcare	12	458,800,000
Flagship Pioneering	11	267,600,000
Canaan Partners	10	277,500,000
Avalon Ventures	10	79,400,000

Also with 10: Morningside Group, The Column Group, Boehringer Ingelheim Venture Fund, Touchstone Innovations. Source: BioCentury: BCIQ

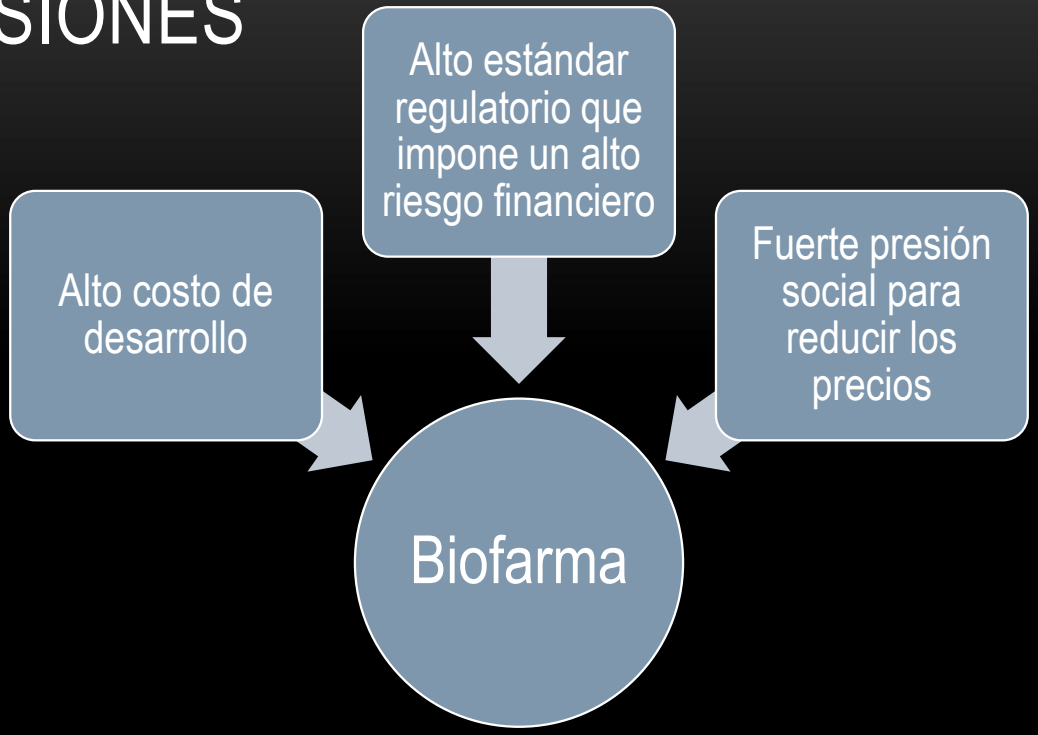
EL PIPELINE DE LOS FONDOS DE INVERSION EN BIOTECH



Las fuentes de capital también están concentradas



CONCLUSIONES



- Nuevo modelo de Negocios:
  - Desarrollo de productos: Medicina personalizada para incrementar eficacia, acortar tiempo de desarrollo y reducir costo. Uso de Biomarcadores, manejo de datos e inteligencia artificial que maximice el beneficio clínico. Enfoque más integral del producto como servicio a largo plazo que justifique los altos precios.
  - Desarrollo de Negocios: Mitigación del riesgo financiero mediante el uso de SPVs. Un producto no es un negocio si no se ofrece en el vehículo empresarial apropiado, con el equipo de dirección adecuado.