Associazione Farmaceutici Industria
Società Scientifica

Regione Lombardia

INTERNATIONAL CONFERENCE

European Clinical Trial day, the future of clinical research: is the 536/14 regulation enough?

Regulatory Authorities, Ethic Committees, Sponsors, Researchers, Sites and Patients

A Paradigm Shift in Clinical Trials

Prof. Claude Farrugia, President EIPG

13th October 2017

Milan, Palazzo Lombardia

A look to the past..

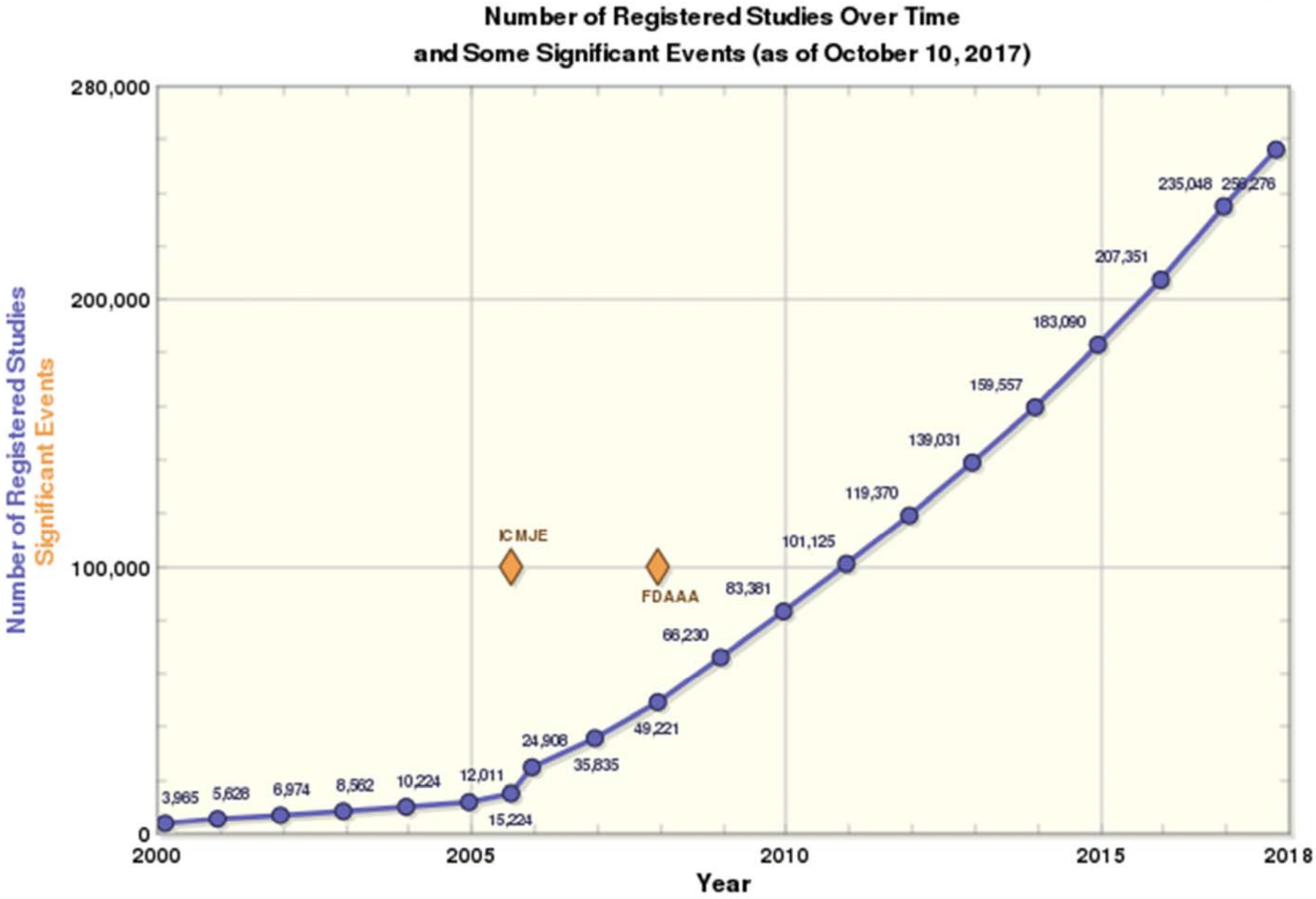
Early clinical development (*Exploratory*)				Full development (*Confirmatory*)		Launch (*Obligatory*)
Final selection compound	**Phase Ia** 40-60 healthy subjects $300,000 6 months	**Phase Ib** 30-50 healthy subjects $300,000 6 months – 1 year	**Phase IIa** 50-200 patients $750,000 9 months – 2 years	**Phase IIb** 200-500 patients $3,500,000 2-3 years	**Phase III** 500-1000+ patients $6,000,000 2-5+ years	**Phase IV** 10000+ patients $10,000,000+ 2-4+ years

…and its precautionary principle

"*The Committee's decided to ban further research until it can be proven your 'wheel' poses no threat to the environment, society or public health*"

The winds of change

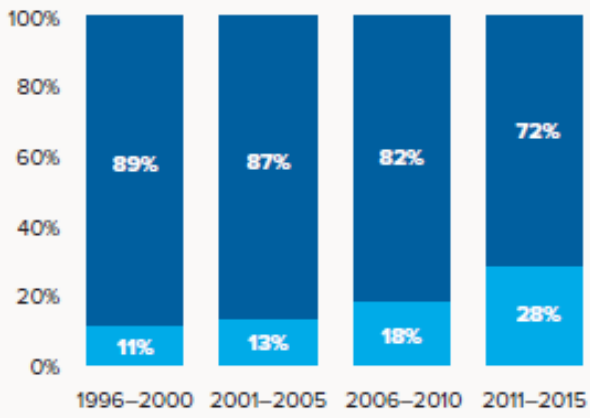
More clinical trials registered

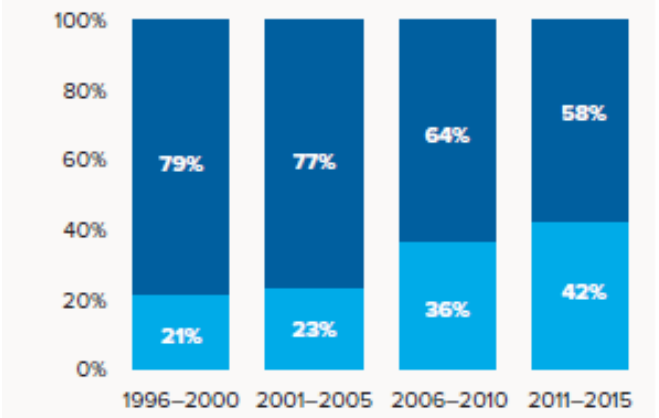


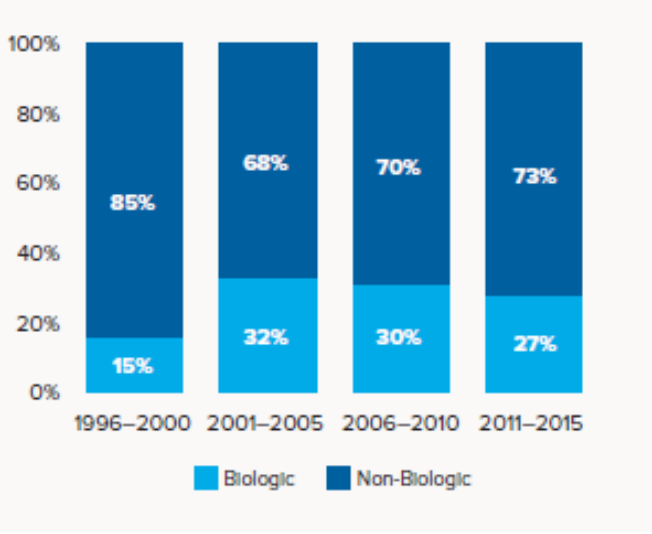
Source: https://ClinicalTrials.gov

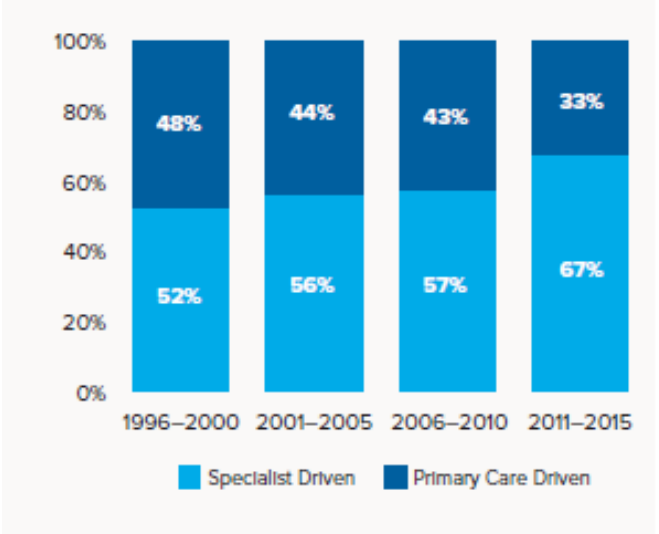
The winds of change

Changes in NAS characteristics over time









Source: QuintilesIMS Institute, Sept 2016

Notes: Primary care and specialist-driven designations refer to the type of physician who initiates or treats using medicines in a given therapy class.

The winds of change

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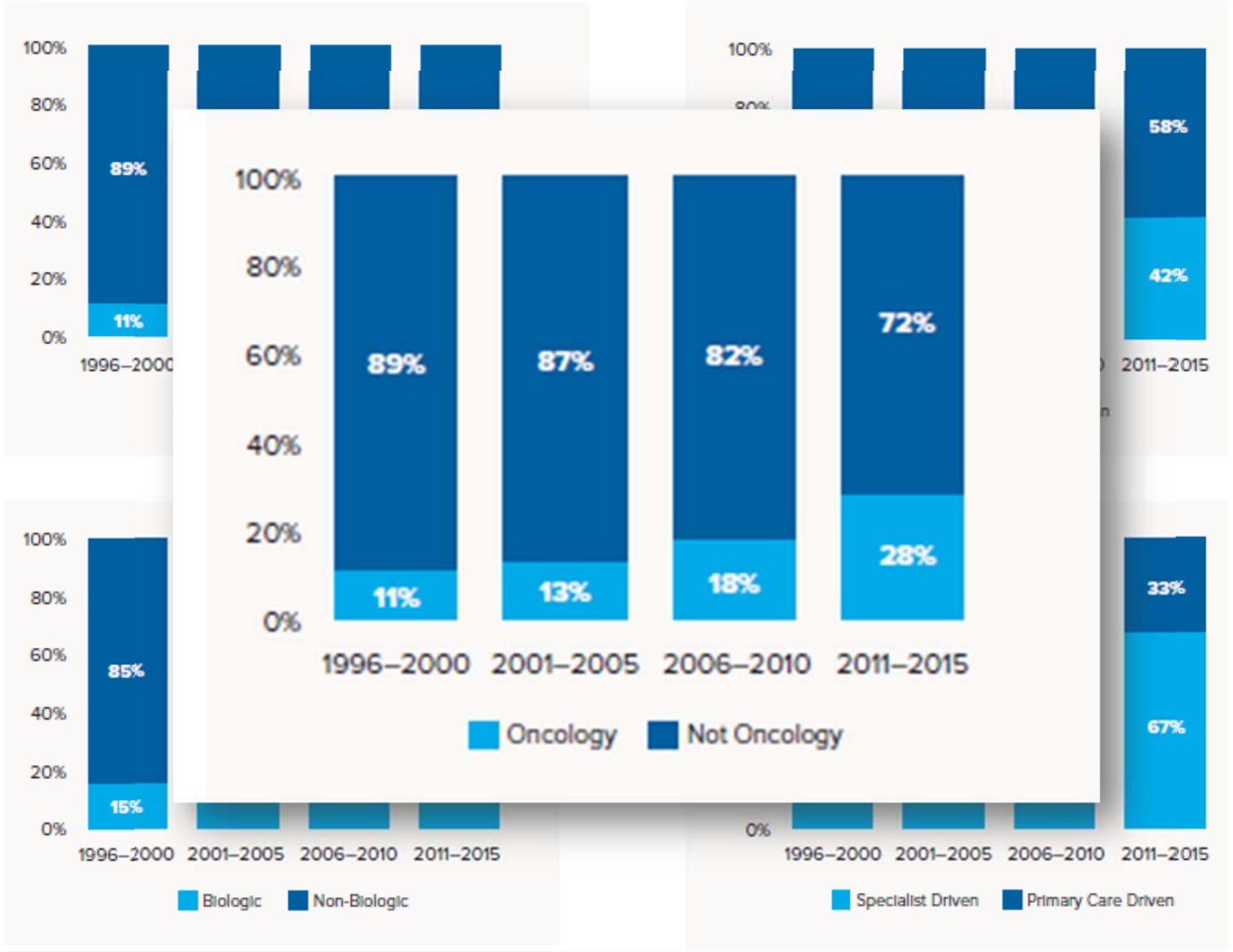

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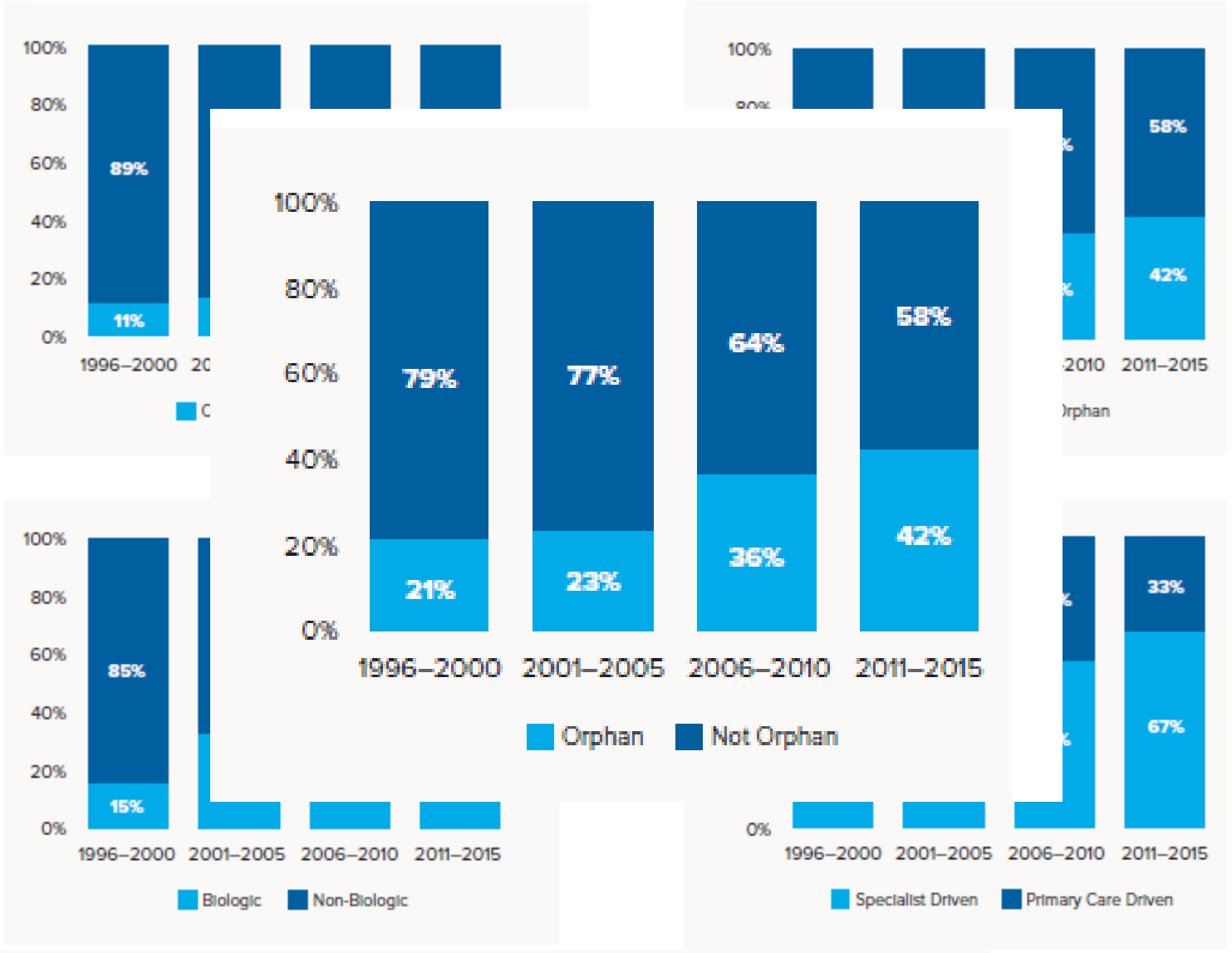

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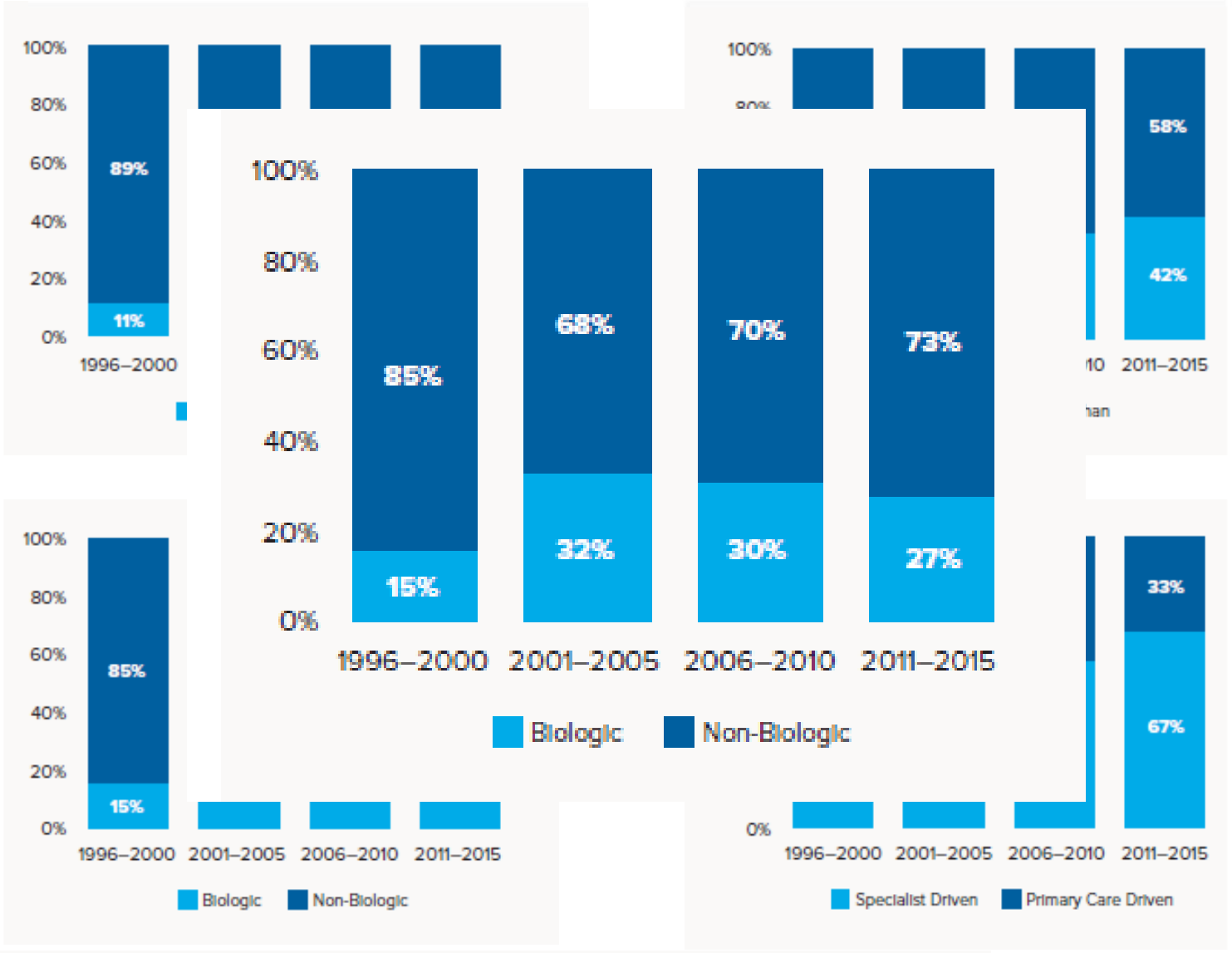

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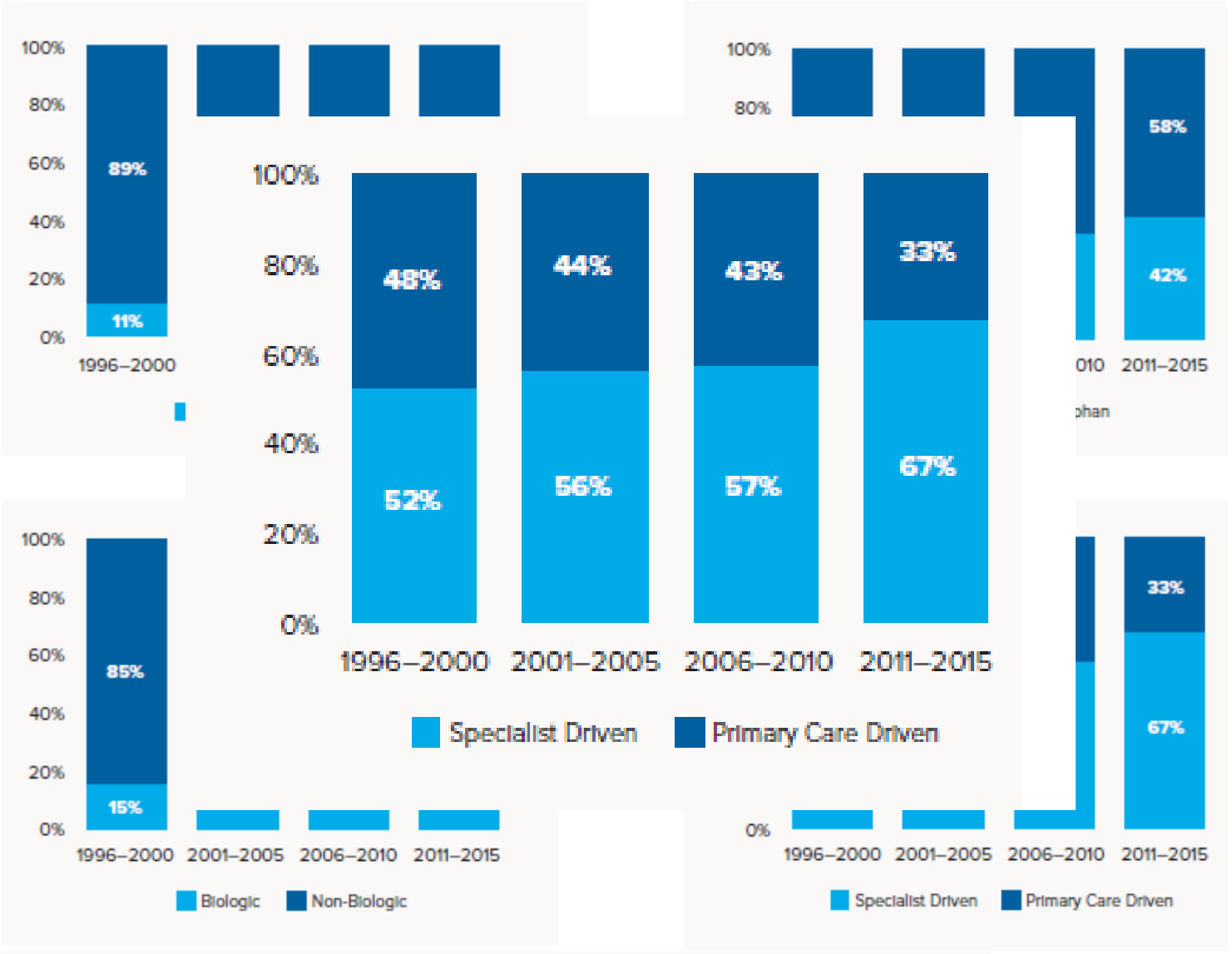

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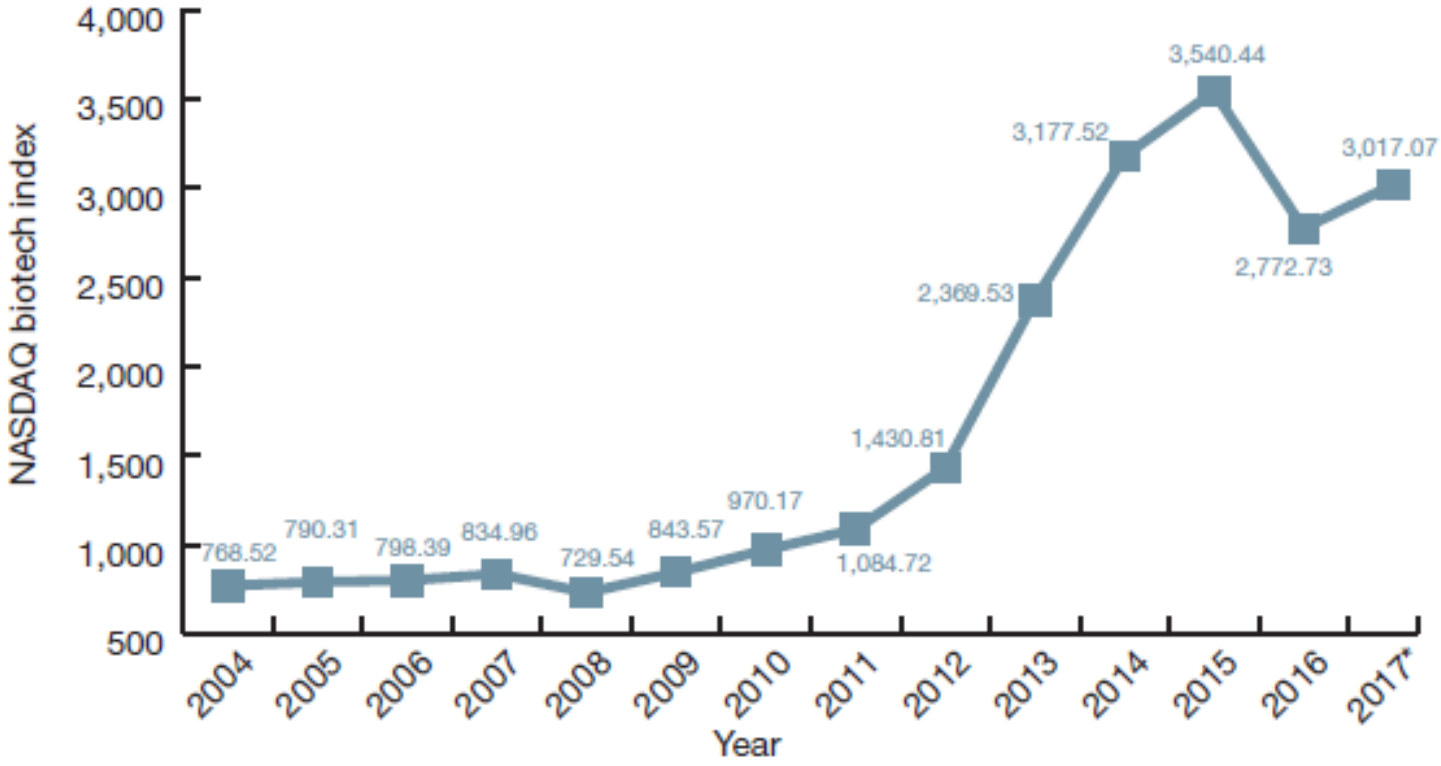
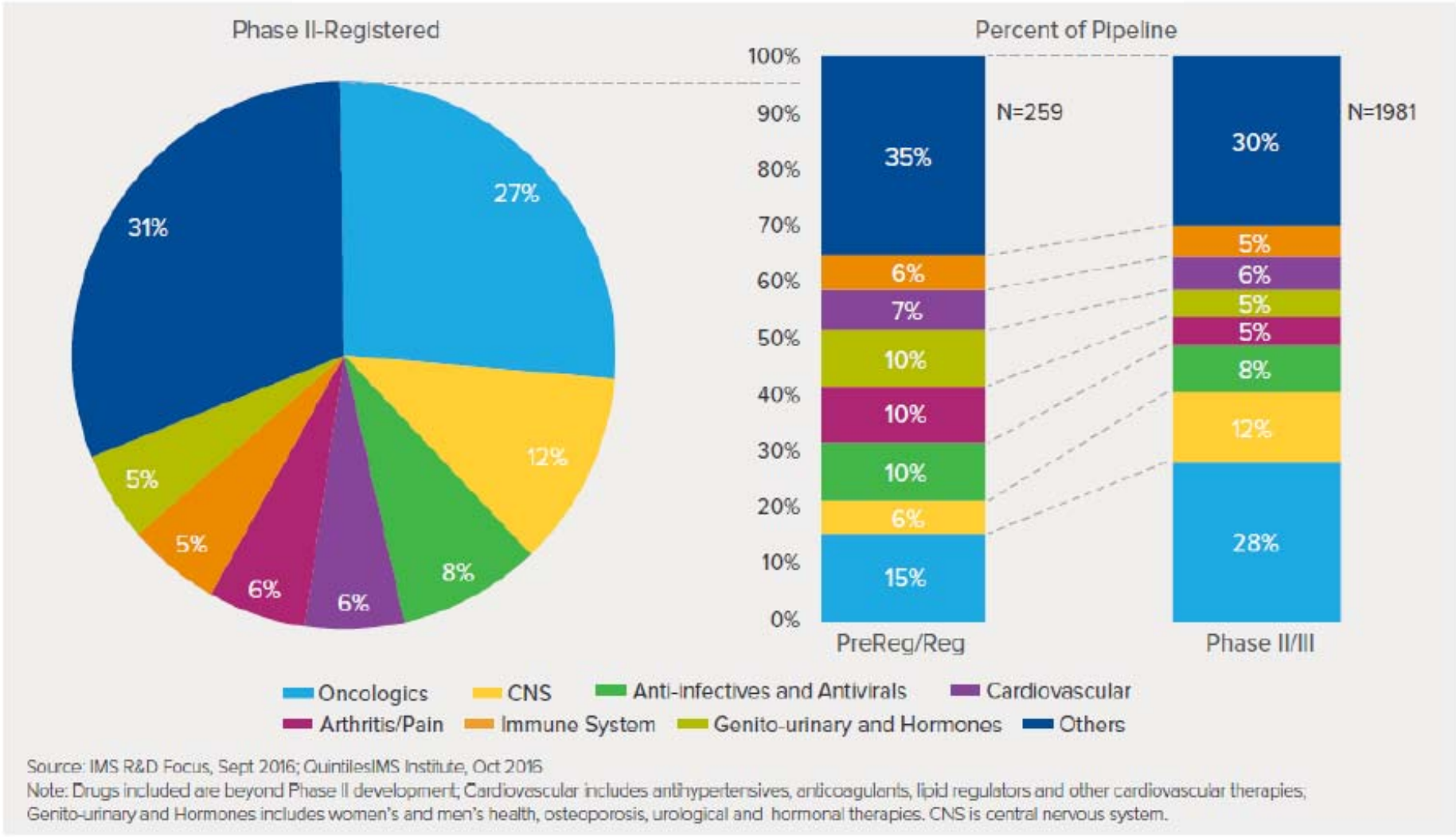


Figure 1 NASDAQ biotech index over time. The data cover each year ending on December 31. *As of 5/26/2017.

Source: Morrison C., Lähteenmäki R., 2017. Public biotech in 2016—the numbers. Nature Biotechnology 35, 623-629.

The winds of change

Global medicines in late stage development in 2016



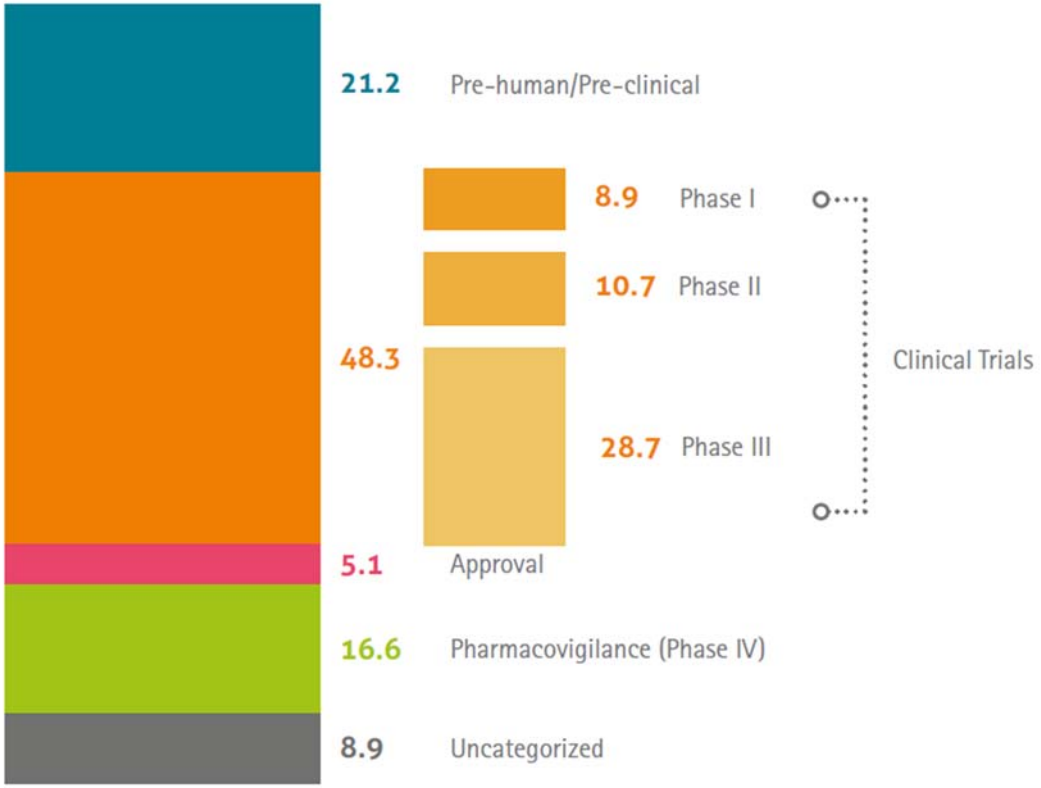
Source: IMS R&D Focus, Sept 2016; QuintilesIMS Institute, Oct 2016

Note: Drugs included are beyond Phase II development; Cardiovascular includes antihypertensives, anticoagulants, lipid regulators and other cardiovascular therapies; Genito-urinary and Hormones includes women's and men's health, osteoporosis, urological and hormonal therapies. CNS is central nervous system.

Outlook for Global Medicines Through 2021: Balancing Cost and Value Report, QuintilesIMS Institute, Oct 2016

Some things don't change

Clinical trials are still the main contributor to R&D cost



Source: PhRMA, Annual Membership Survey 2016 (percentages calculated from 2014 data; total values may be affected by rounding)

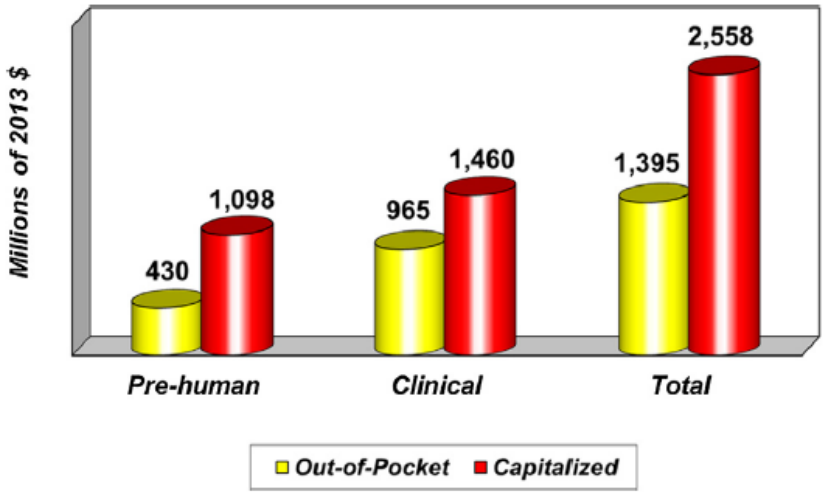


Fig. 2. Pre-human phase, clinical phase, and total out of-pocket and capitalized costs per approved new compound.

Source: DiMasi J.A., Grabowski H.G., Hansen, R.W., 2016. Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics 47, 20-33.

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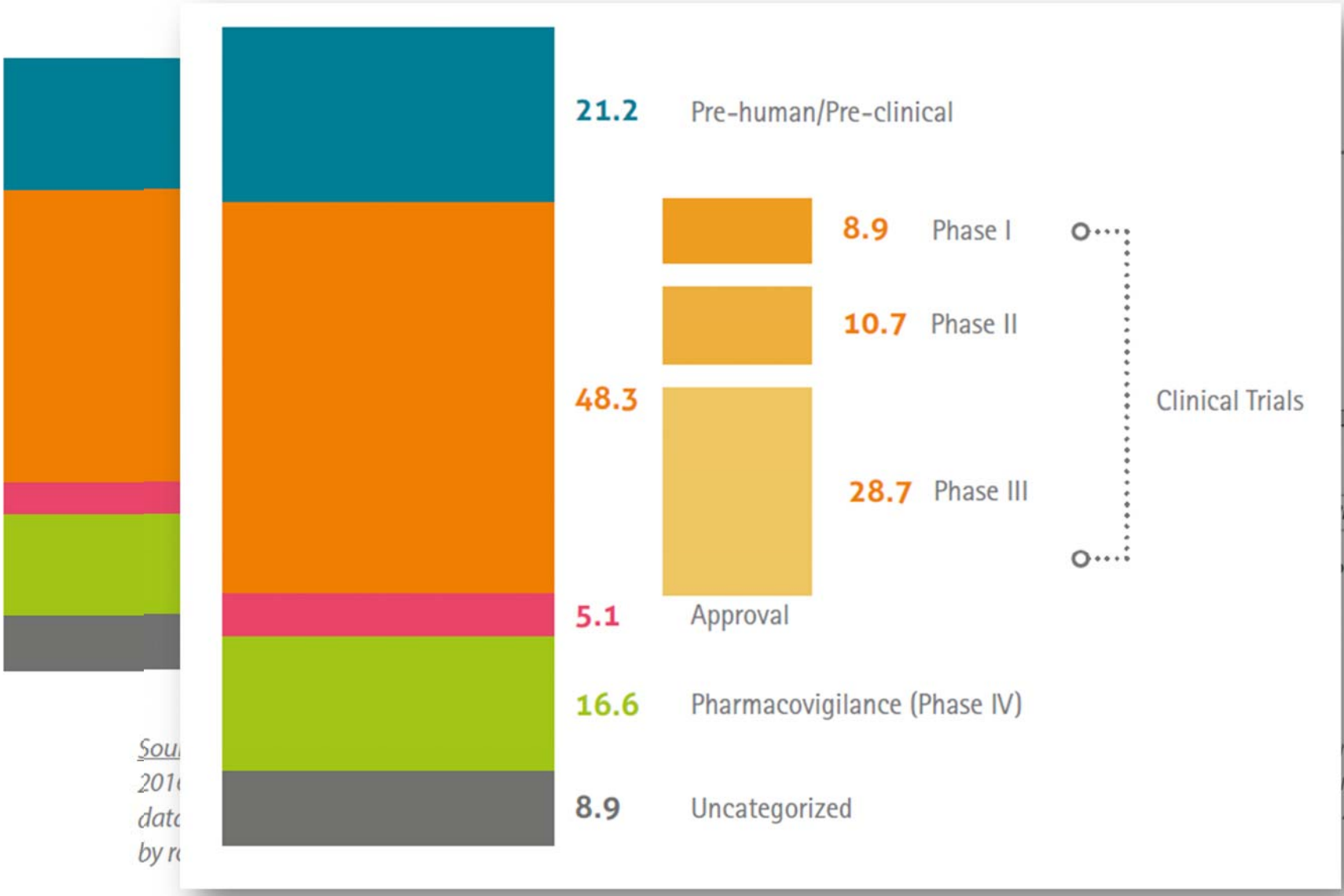

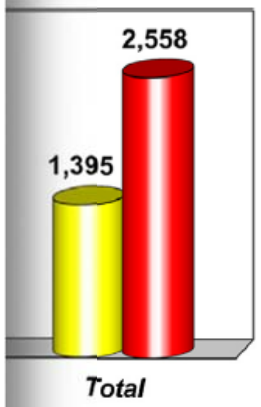

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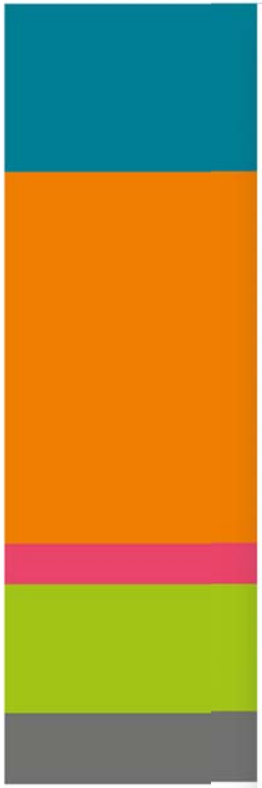

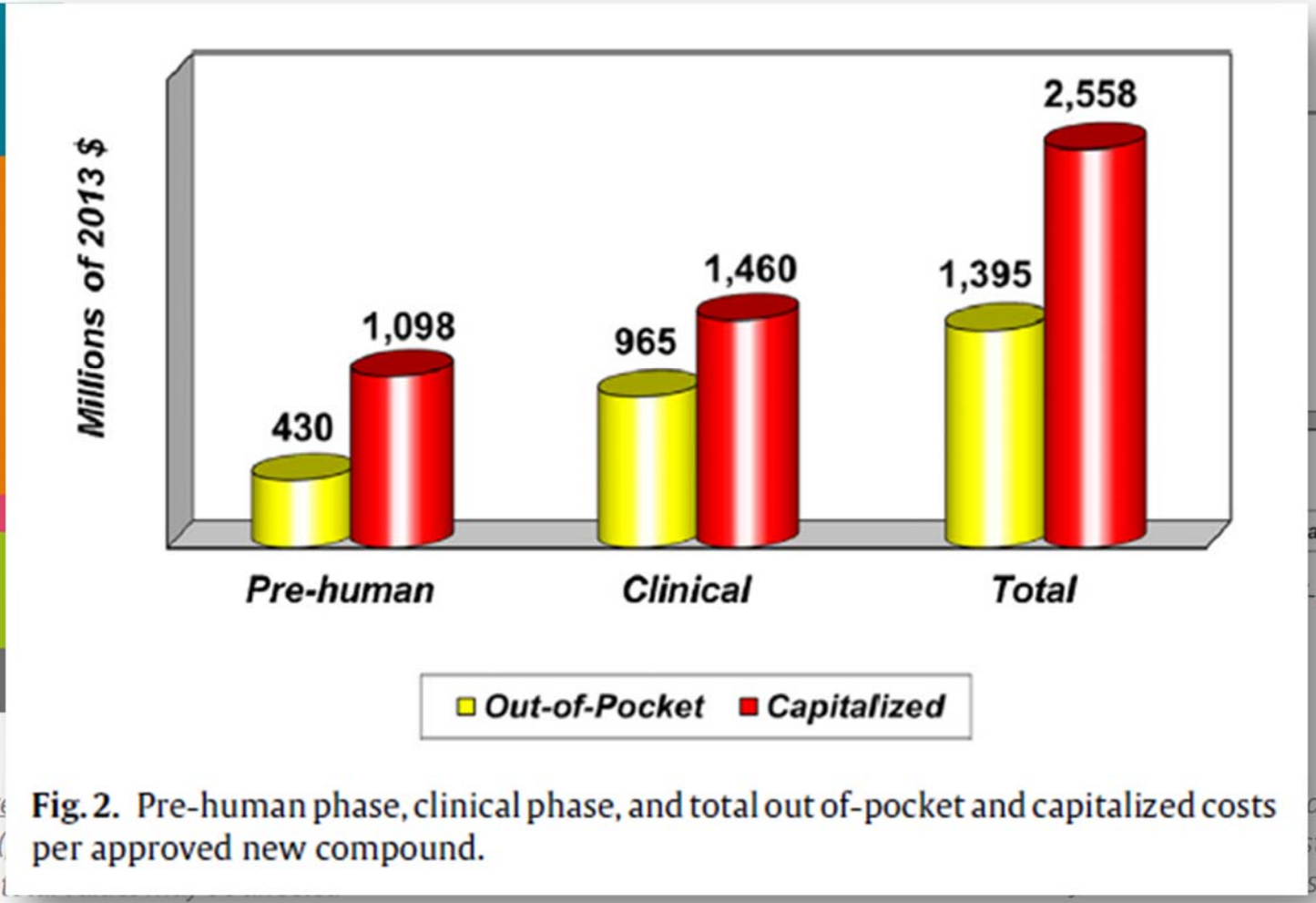

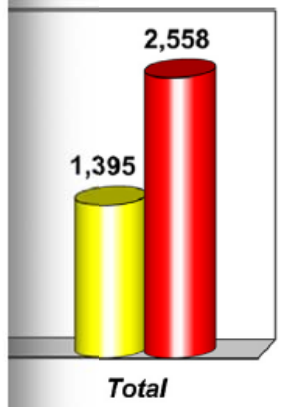

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Some things don't change

Success is rewarding but failure is costly

Most Valuable R&D Projects (Ranked by NPV) in August 2016 Which Have Since Been Approved or Suffered Setbacks

Source: Evaluate, May 2017

Change vs. Aug 2016	Product	Company	Status (Aug 2016)	Status Change Since Aug 2016	Aug 2016 NPV ($m)	Today's NPV ($m)	Change vs. Aug 2016 (%)
Approved	**Imfinzi**	AstraZeneca	Phase III	Marketed	8,276	**13,069**	58%
	Kisqali	Novartis	Phase III	Marketed	6,370	**6,921**	9%
	Amjevita	Amgen	Filed	Marketed	6,273	**2,549**	-59%
	Ocrevus	Roche	Filed	Marketed	16,965	**18,242**	8%
	Dupixent	Sanofi	Phase III	Marketed	12,884	**18,775**	46%
				Sub-Total	50,768	**59,556**	17%
Setback	**Solanezumab**	Eli Lilly	Phase III	Abandoned, Phase III	5,577	**0**	-100%
	Fovista	Ophthotech	Phase III	Clinical trial setback	5,514	**164**	-97%
	Verubecestat	Merck & Co	Phase III	PI/III trial discontinuation	5,219	**1,748**	-67%
	JCAR017	Juno Therapeutics	Phase II	CAR-T class effect concerns	4,836	**3,676**	-24%
	Veliparib	AbbVie	Phase III	Missed PIII trial endpoints	7,502	**1,321**	-82%
	Mongersen	Celgene	Phase III	Disappointing trial results	4,719	**3,335**	-29%
				Sub-Total	**28,648**	**6,908**	**-76%**
Total					**79,416**	**66,465**	**-16%**

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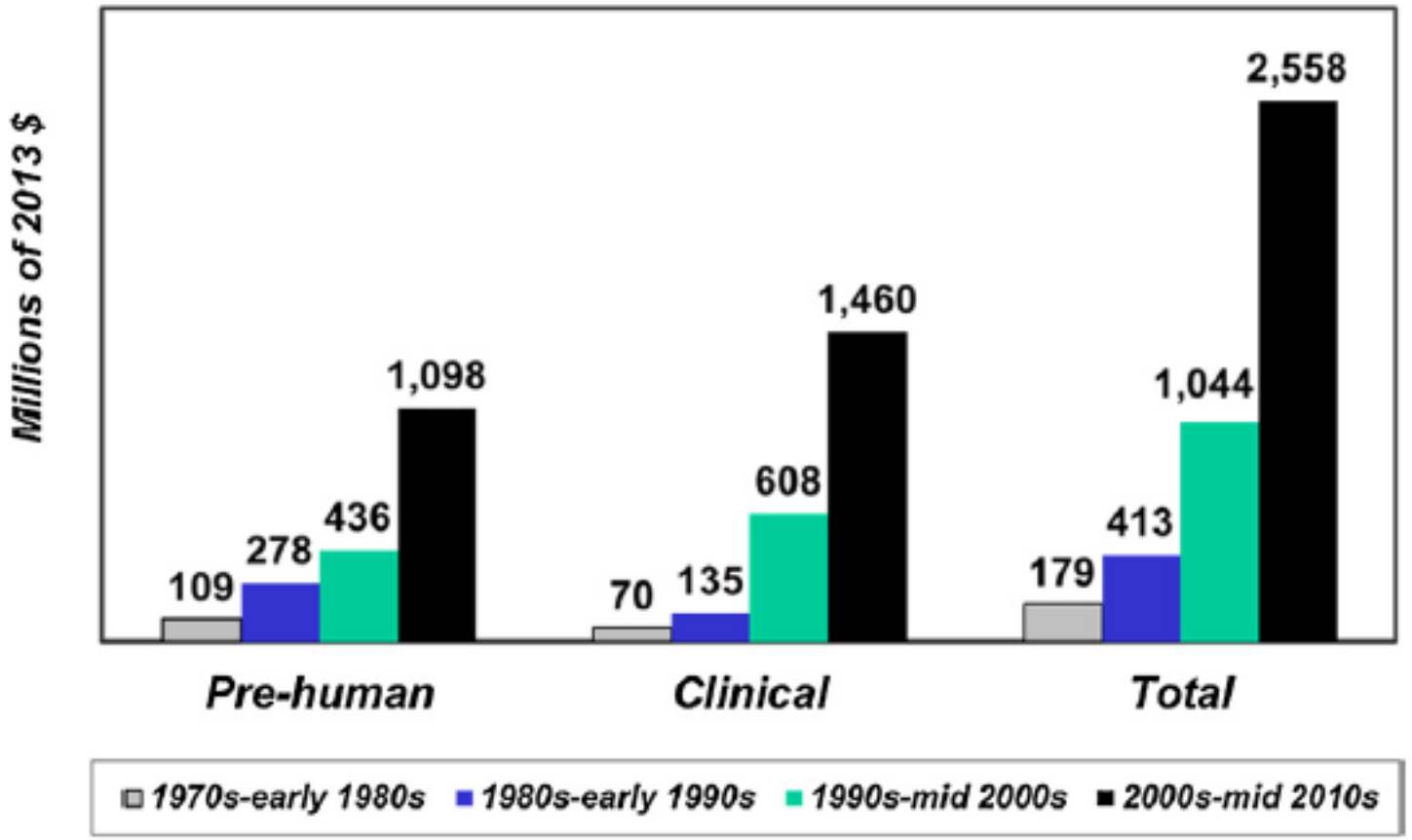
Headwinds of change

Drug development is getting costlier



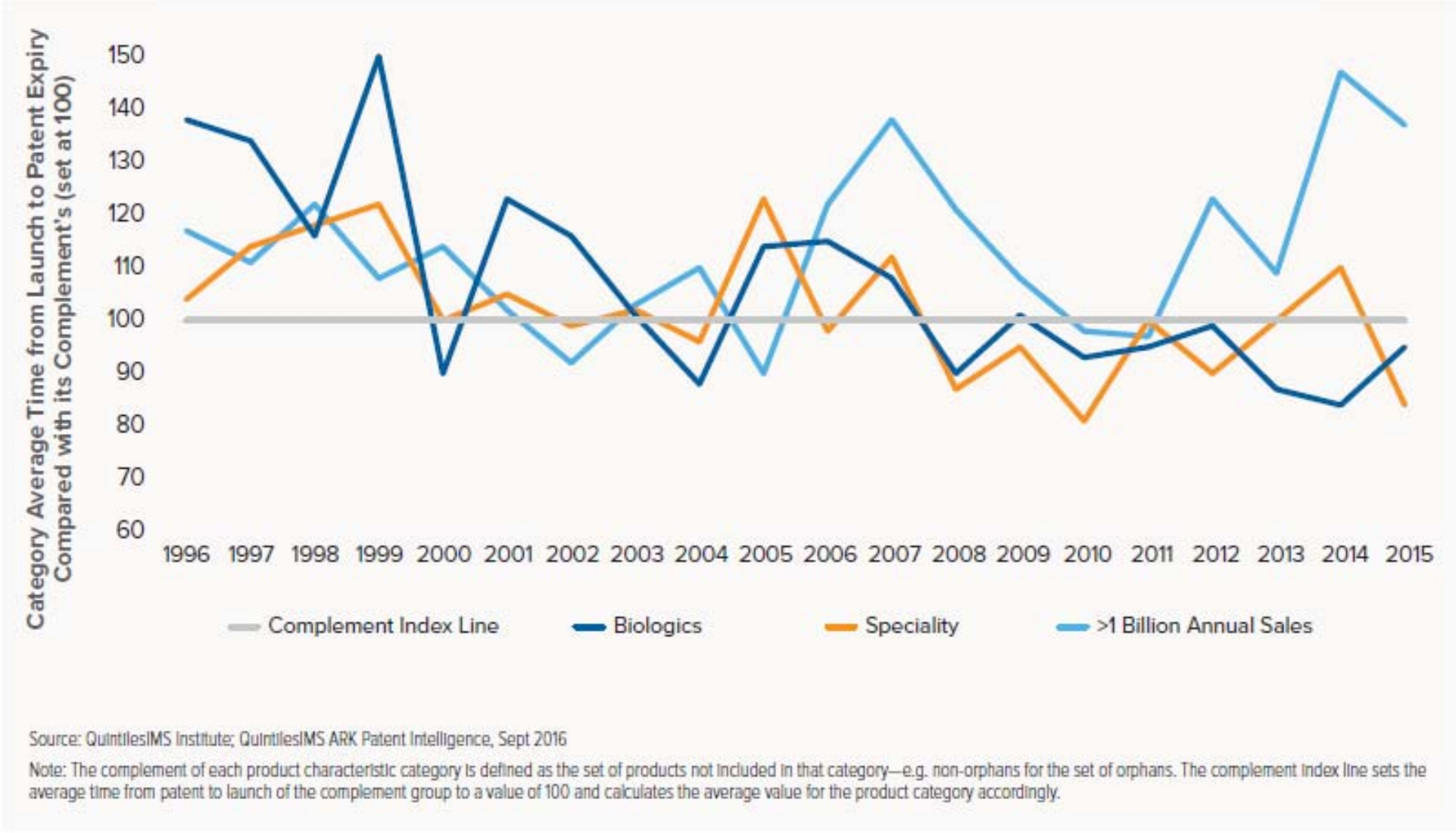
Sources: 1970s-early 1980s, Hansen (1979); 1980s-early 1990s, DiMasi et al. (1991); 1990s-mid 2000s, DiMasi et al. (2003); 2000s-mid 2010s, Current Study

Fig. 3. Trends in capitalized pre-human, clinical and total cost per approved new drug.

Source: DiMasi J.A., Grabowski H.G., Hansen, R.W., 2016. Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics 47, 20-33.

Headwinds of change

Average time from launch to patent expiry for new active substances



Source: QuintilesIMS Institute; QuintilesIMS ARK Patent Intelligence, Sept 2016

Note: The complement of each product characteristic category is defined as the set of products not included in that category—e.g. non-orphans for the set of orphans. The complement index line sets the average time from patent to launch of the complement group to a value of 100 and calculates the average value for the product category accordingly.

Headwinds of change

Trends in biotech financing

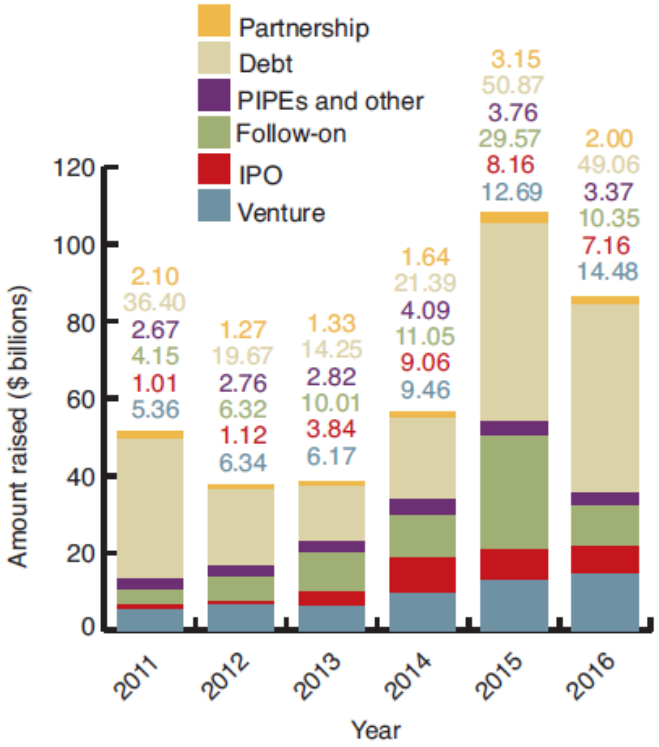


Figure 3 Global biotech industry financing. PIPEs, private investment in public equity. Sources: BCIQ BioCentury Online Intelligence. BioCentury updates its financing data on an ongoing basis.

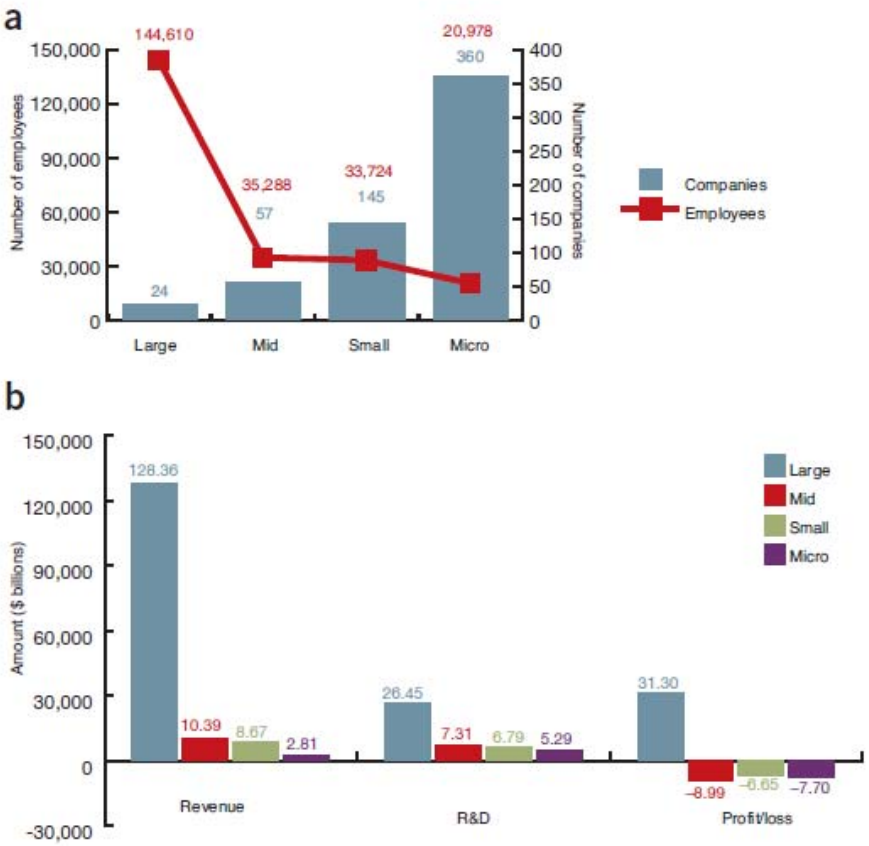
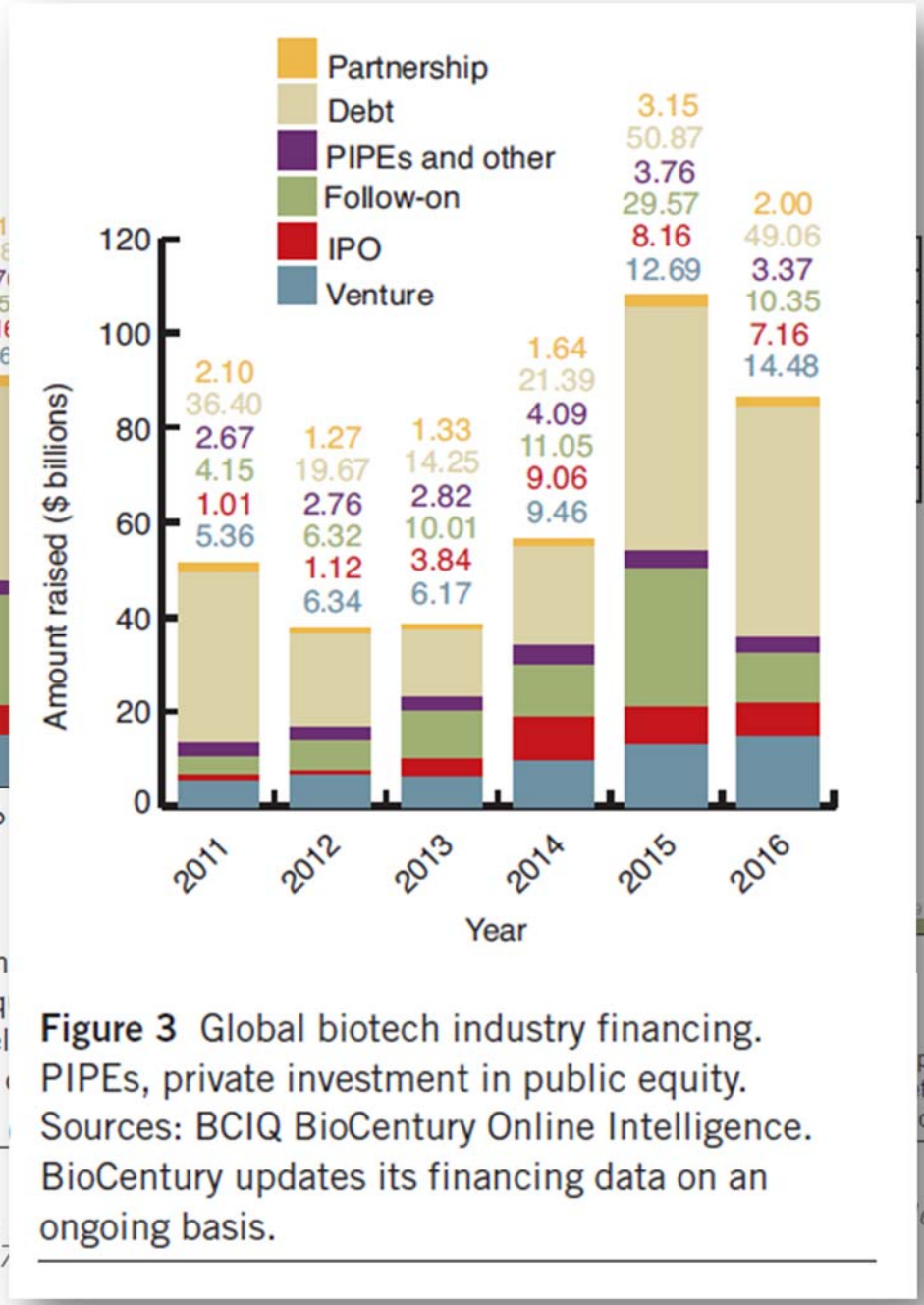


Figure 4 Public biotech barometers. (**a**) Public biotech company revenue, R&D spending, net profits and loss. (**b**) Number of companies and employees by market cap. Large cap, ≥$5 billion; mid-cap, $1 billion < $5 billion; small cap, $250 million to < $1 billion; micro-cap, <$250 million.

Source: DiMasi J.A., Grabowski H.G., Hansen, R.W., 2016. Innovation in the pharmaceutical industry: New estimates of R&D costs. Journal of Health Economics 47, 20-33.

Headwinds of change

Trends in biotech financing



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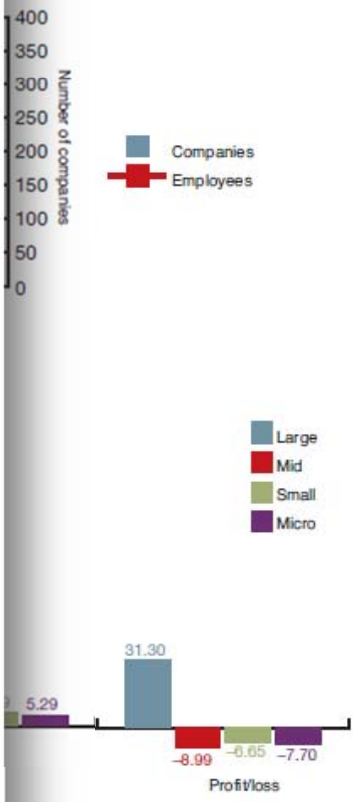

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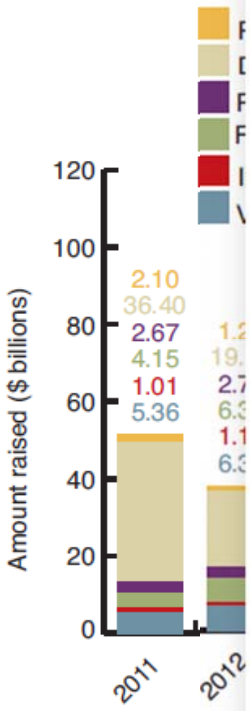

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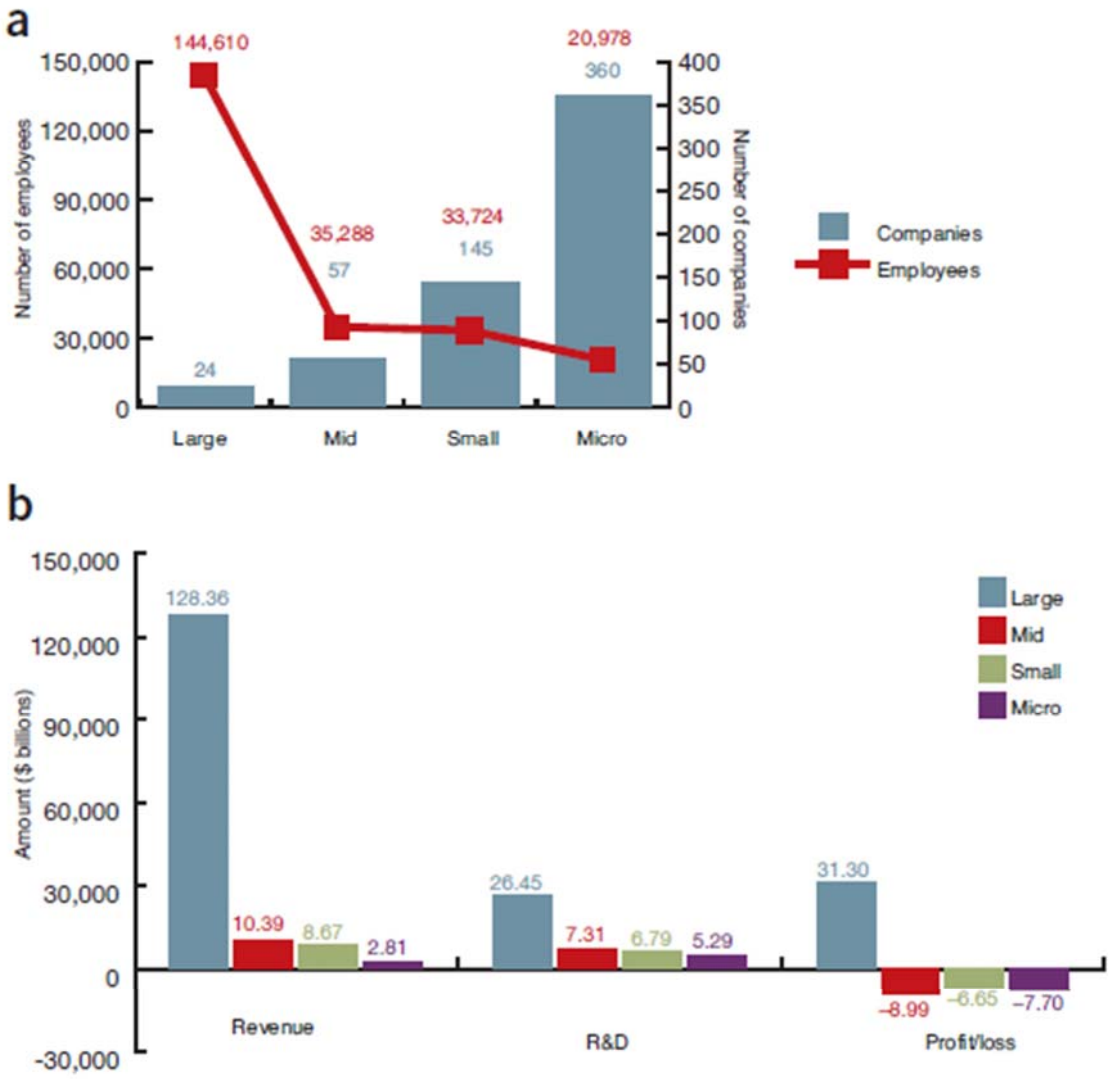

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Source: DiMasi J.A costs. Journal of H

f R&D

A paradigm shift

The patient at the centre

Pharma 3.0

From drugs to healthy outcomes

Drivers of change

- R&D productivity
- Patent cliff
- Globalization
- Demographics
- Pricing & reimbursement
- Health care reform
- Health IT
- Consumerism
- Value mining

Business Models

Value proposition

- **Pharma 1.0** — Blockbuster drugs
- **Pharma 2.0** — Diversified drug portfolios
- **Pharma 3.0** — Healthy outcomes

Customer

Physician

Payor

Patient

ERNST & YOUNG
Quality In Everything We Do

A paradigm shift

Patients as partners

Patient involvement in medicines R&D

High expertise in disease area required

Research Priorities
- Setting Research Priorities
  - gap Analysis
  - early horizon Scanning
  - matching unmet needs matched with research
  - defining patient-relevant added value and outcomes

Research Design and Planning
- Protocol Synopsis
  - design
  - target population
- Design of Protocol
  - relevent endpoints
  - benefit/risk balance
  - in-/exclusion criteria
  - diagnosis procedures
  - Quality of life and patient reported outcomes
  - ethical issues,
  - data protection
  - mobility issues/logistics
  - adherence measures

Research Conduct and Operations
- Trial steering committee
  - protocol follow up
  - Improving access
  - adherence
- Information to trial participants
  - protocol amendments
  - new safety information
- Investigators Meeting
  - Trial design
  - recruitment
  - challenges
  - opportunities can trigger amend-ments
- Data & Safety Monitoring Committee
  - benefit/risk
  - drop-out issues
  - amendments

Dissemination, Communication, Post-approval
- Regulatory Affairs
  - MAA evaluation
  - EPAR summaries
  - lay summary of results
  - package leaflets
  - updated safety communication

Medium expertise in disease area required

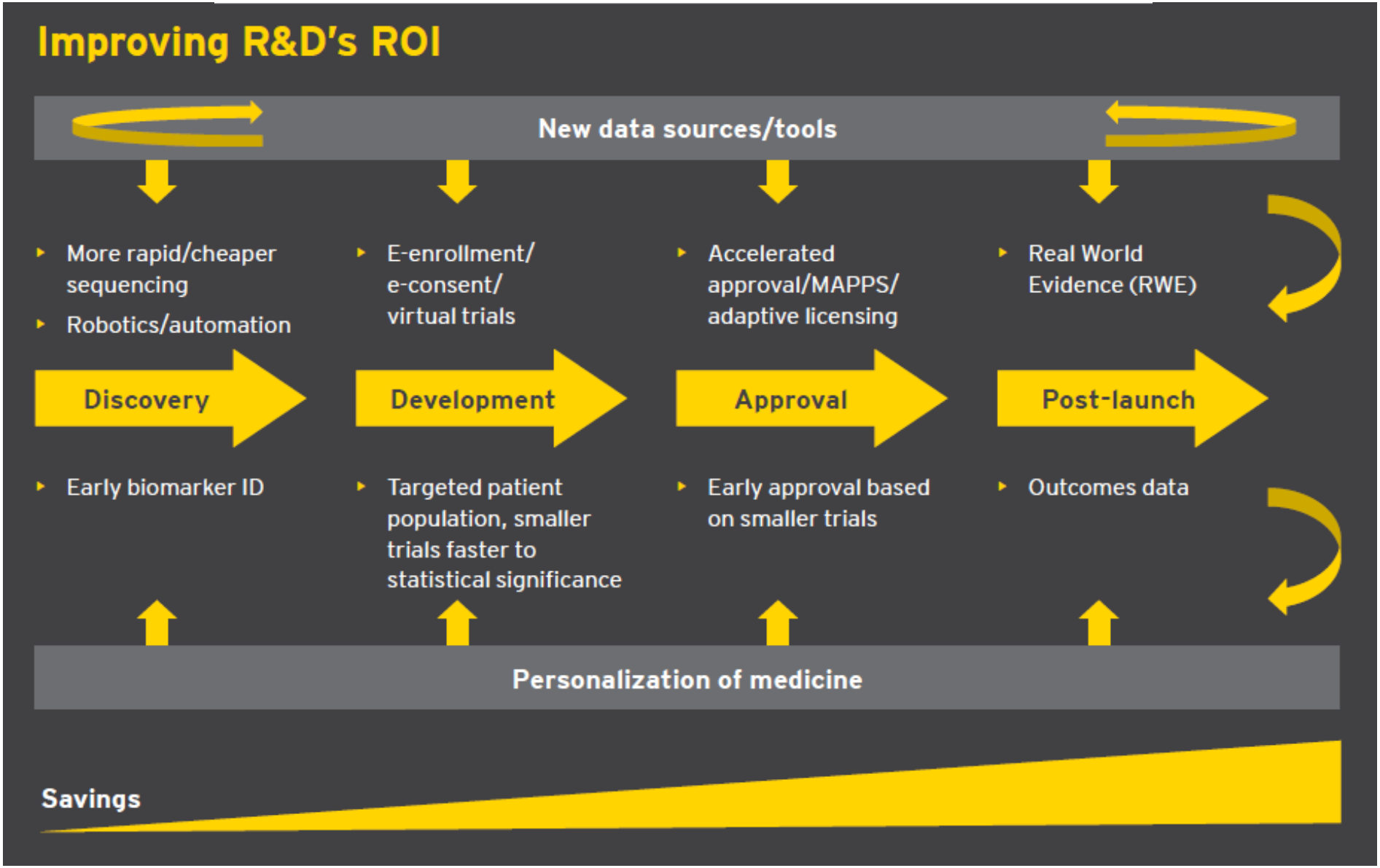
- Fundraising for research
- Practical Considerations
  - contractual issues
  - travel expenses
  - support for family members
  - mobility
- Patient Information
  - content
  - visual design
  - readability
  - language
  - dissemination
- Ethical Review
  - content
  - visual design
  - readability
  - language
- Informed Consent
- Study reporting
  - summary of interim fresults
  - dissemination in patient community
- Health Technology Assessment
  - assessment of value
  - patient reported outcomes
  - patient priorities
- Post-study communication
  - contribution to püublications
  - diseemination of research results to patient community / professionals

EUPATI
European Patients' Academy on Therapeutic Innovation
www.eupati.eu

Geissler, Ryll, Leto, Uhlenhopp
EPALCO/EUPATI (2015, unpublished)

A paradigm shift

From clinical trials to the real world



A paradigm shift

From clinical trials to the real world

	Efficacy (Clinical Trail Data)	Effectiveness (Real-World Data)	Post-Marketing Surveillance (PMS)
Objective	Works under ideal circumstances	Works under usual circumstances	Works under customary condition of the drug use
Setting/Design	Controlled clinical trial	Real-world clinical practice	Controlled/spontaneous/ cohort/case control studies
Purpose	Regulatory approval (FDA)	Drug performance in real world	Monitoring the safety of the drug
Intervention or Treatment	Fixed regimen	Flexible regimen	Flexible regimen
Comparator	Placebo	Active comparator/usual care	Active
Subjects	Homogenous/highly selective (stringent inclusion/exclusion criteria)	Heterogeneous/any subjects	Heterogeneous/any subjects
Compliance	High	Low to high	Low to high

What do we need?

Technology tectonics

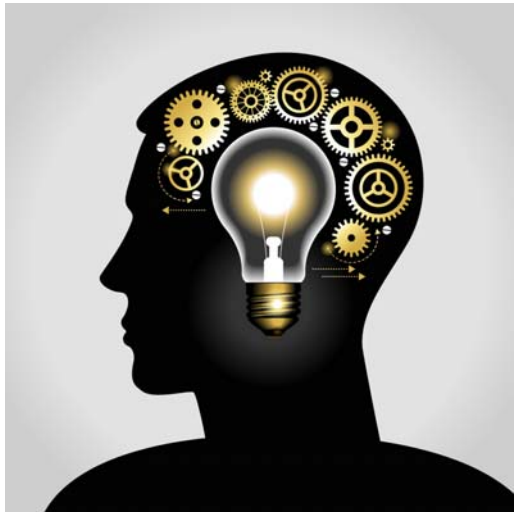
Quality transparency

Collaboration and continuity

What do we need?

Technology tectonics

What do we need?



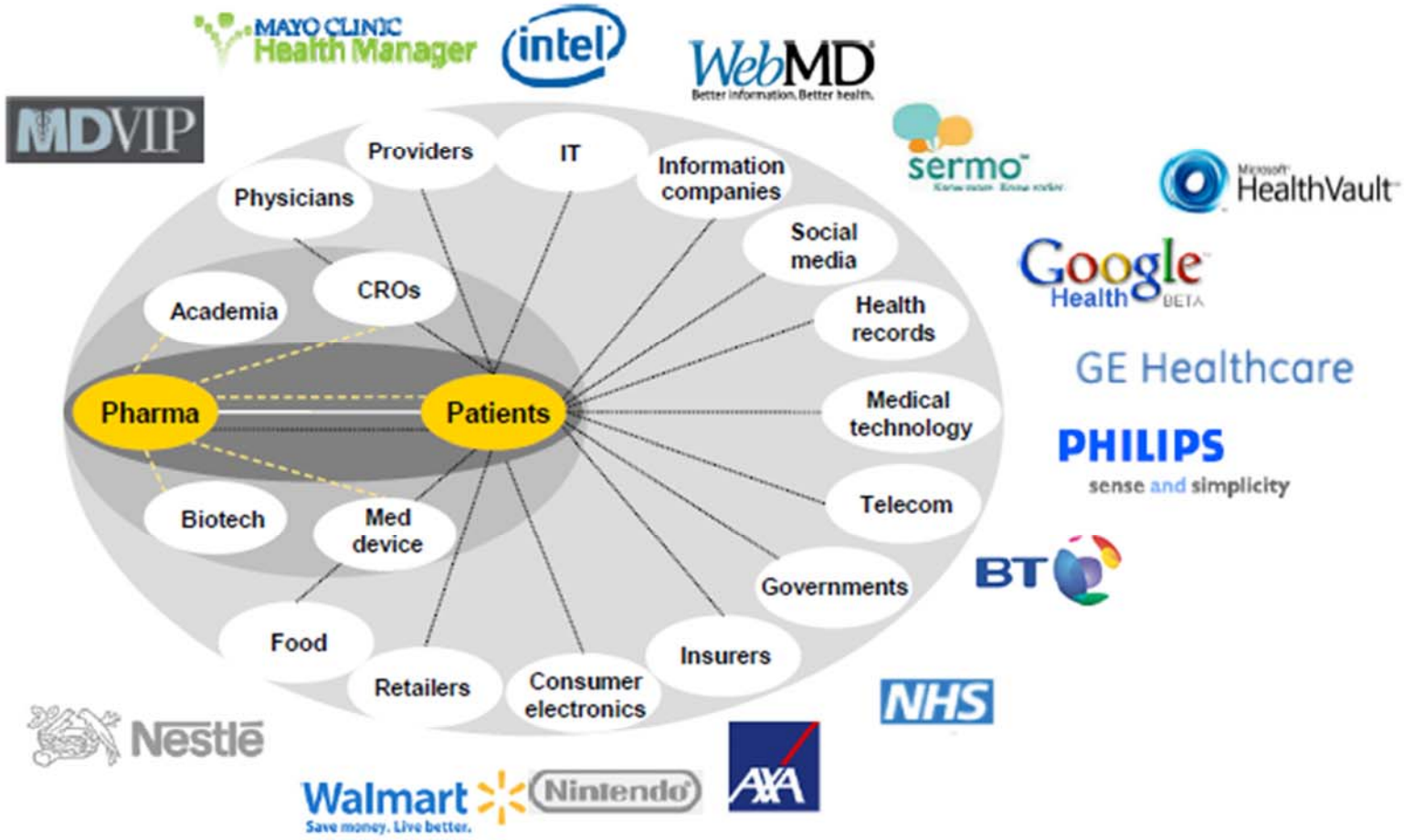
Quality transparency

"I know nothing about the subject,
but I'm happy to give you my expert opinion."

What do we need?

Collaboration and continuity

What do we need?



Pharma 1.0 (drugs) Pharma 2.0 (diversified drug portfolios) Pharma 3.0 (outcomes)

Ernst & Young
Quality In Everything We Do

Thank you for your attention