Drug Discovery, Development and Commercialization, 2016

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Lecture Objectives

- Course Objectives
- Pharmaceutical & Biotechnology Industry Landscape 2014 - 2015
- 2016 Global Outlook: What Will the Future Potentially Look Like?
- Patient Centric Drug Discovery & Development

DDC Course Objectives

- Drug Discovery Process
  - From target to Investigational New Drug Application (IND)
  - Pharmaceutics & Life Cycle Strategic Plan
- Clinical Development
  - IND to New Drug Application (NDA) submission
  - Clinical study design
- Regulatory Requirements to File an IND and an NDA in the US & Europe
- Intellectual Property Strategy
- Commercialization Strategies
  - Marketing strategy; Managed markets
  - Strategic partnership and business development
- Work in Multifunctional Teams

Pharmaceutical & Biotechnology Industry Landscape 2014 -2015

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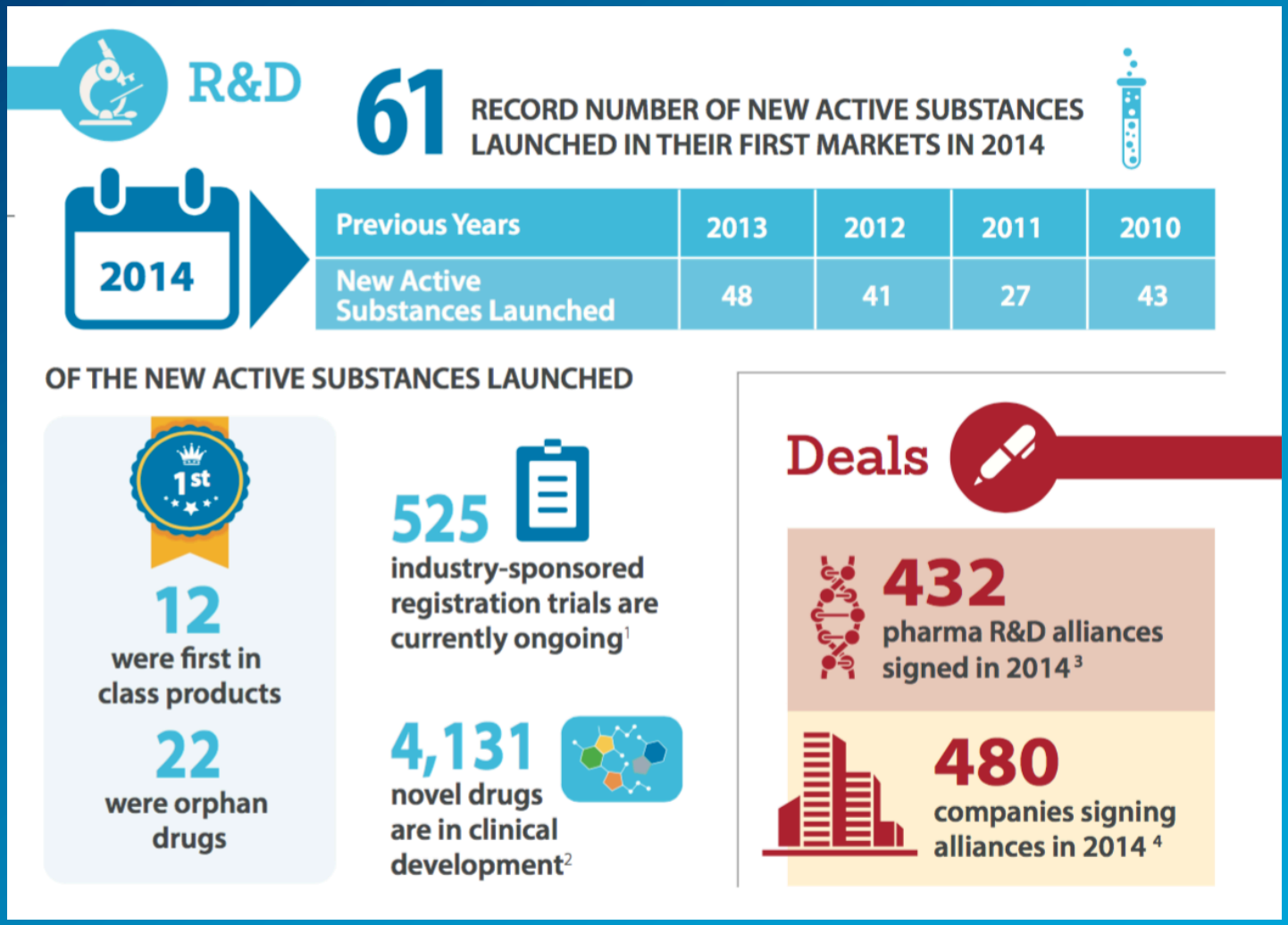
R&D in 2014



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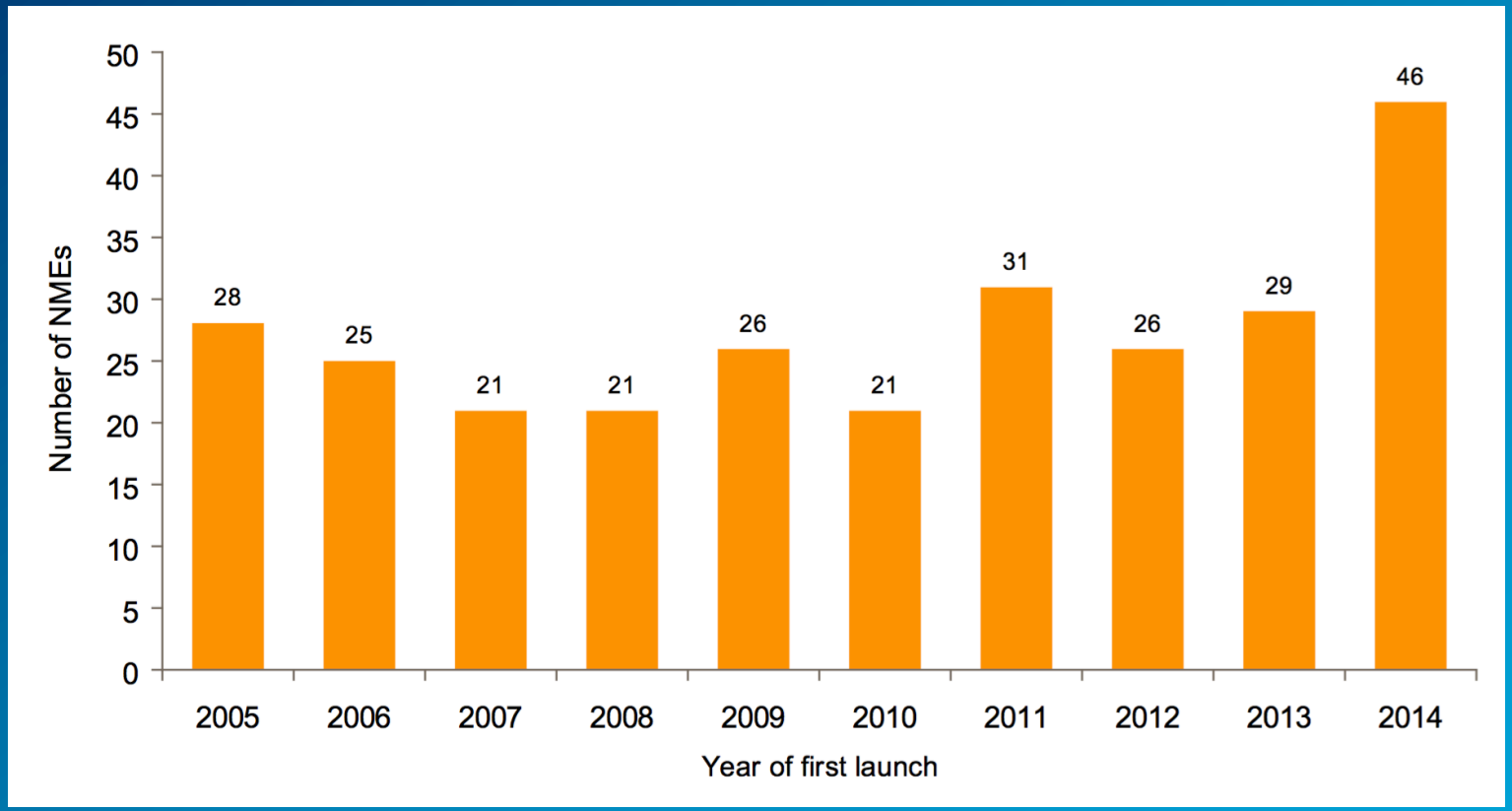
Number of NME First-World Launches, 2005 TO 2014



In 2014 67% of the first launches were specialty drugs for cancer, HCV and eye disorders

- 1/3 of all launches were for rare indications
- 11 NMEs in oncology, 7 received orphan drug status

Source: 2015 CMR International Pharmaceutical R&D Factbook

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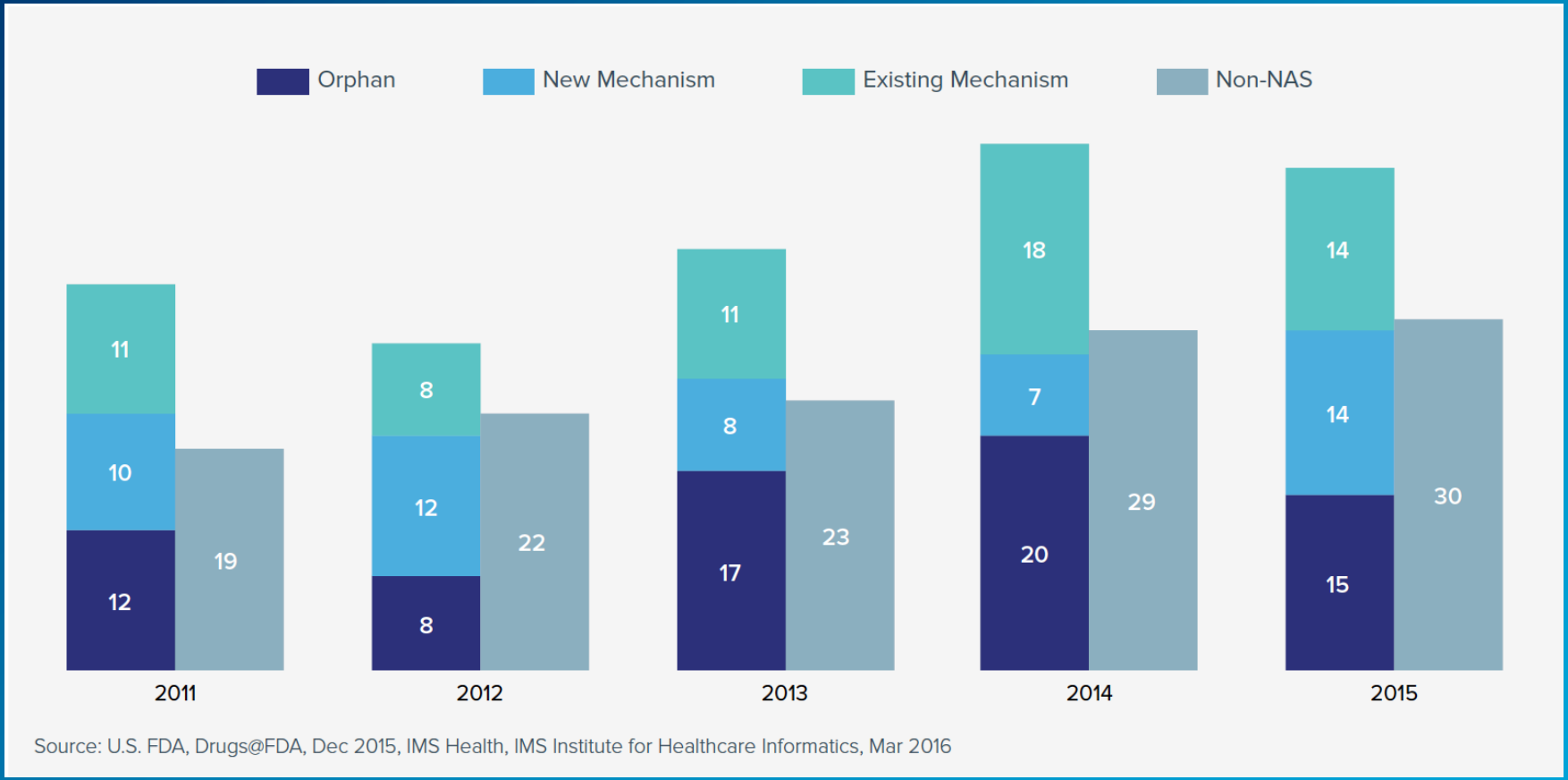
2015 Record Year
FDA NME & BLA Approvals 2004 - 2015



Source: U.S. FDA, Drugs@FDA, Dec 2015, IMS Health, IMS Institute for Healthcare Informatics, Mar 2016

- **2015 FDA approved 43 New active substances NME & BLA**

"In the next four years there will be 225 new drug approvals and most of them in cancer-related therapeutic spaces" IMS

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FDA Drug Approvals 2014 - 2015
A Barometer of Industry Innovation

- The highest number of New Molecular Entity first-world launches in the last decade registered in 2015.
- A decline in the early development pipeline coupled with a growth in the late development pipeline and success rates suggestive of the industry's ability to "fail fast, fail cheaply"
- As of December 14, 2015, FDA has given 37 approvals to drugs designated as Breakthrough Therapies, 17 of them first time approvals for novel drugs.
- The late phase pipeline holds 2,320 novel products and 43-49 New Active Substances are expected to be launched on average for each of the next five years.

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/NDAandBLAApprovalReports/ucm373420.htm

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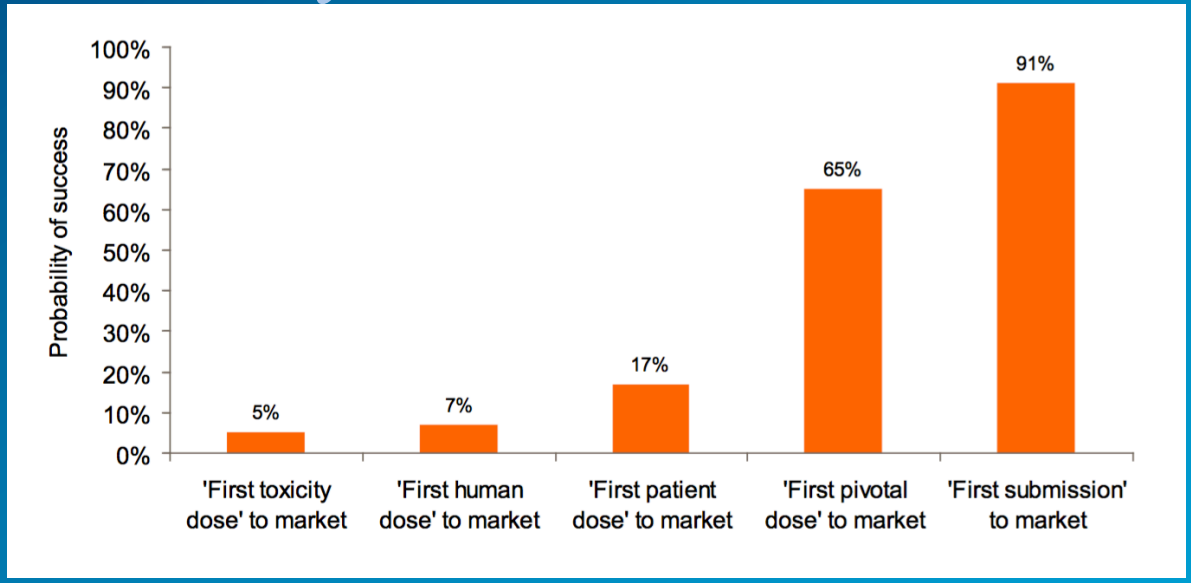
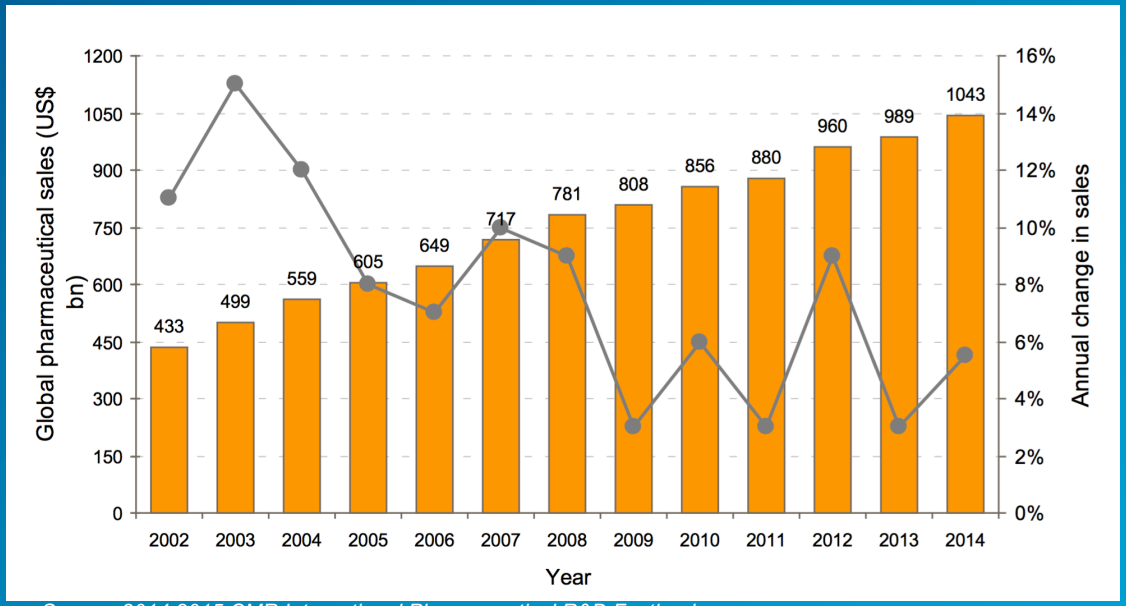
Probability of Success to Market

Calculated using success rates between phase for active substances entering phase between 2008 and 2010 and year of assessment 2013



Global Pharmaceutical Sales



$1 trillion mark for the first time by the end of 2014

Source: 2014 2015 CMR International Pharmaceutical R&D Factbook

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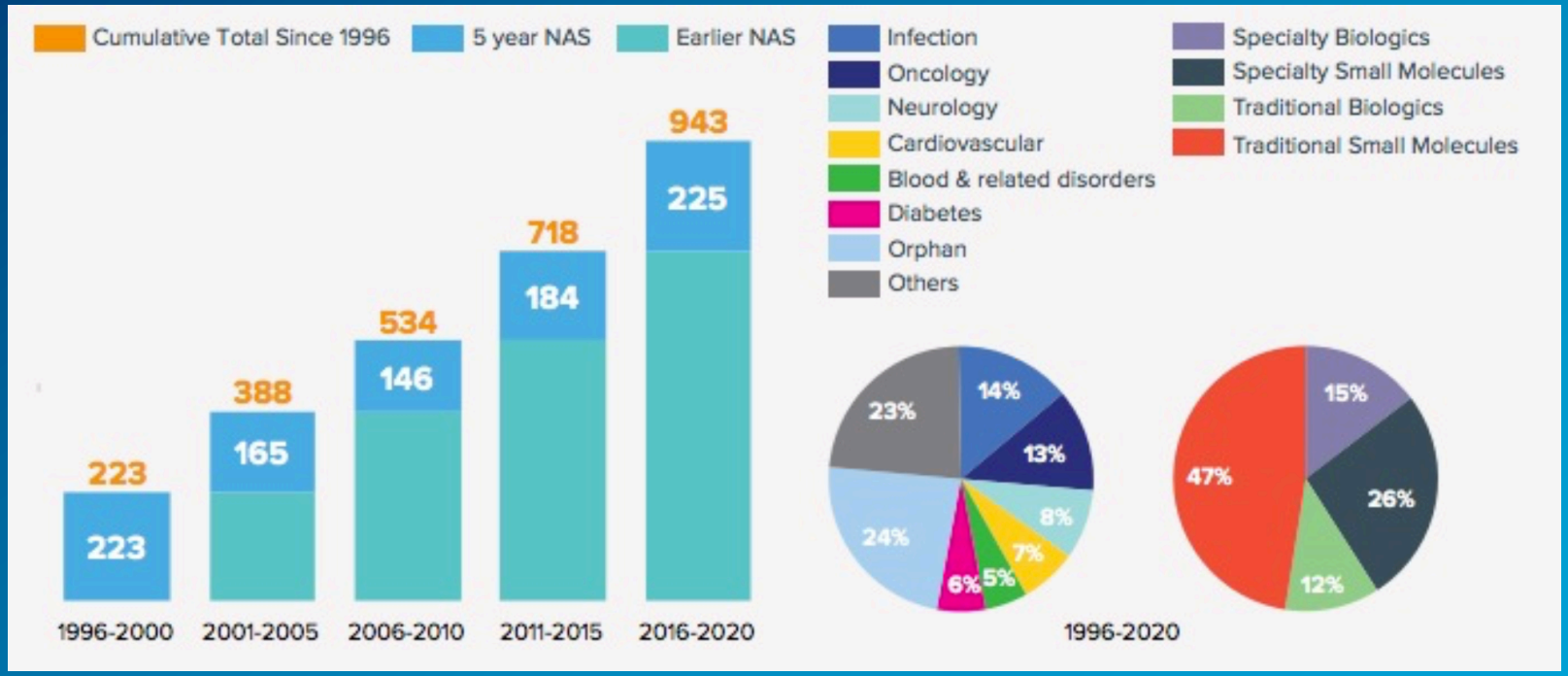
New Active Substances Available Since 1996



Key issues:

- Obtaining the greatest value for the dollars we spend on drugs
- Having a vital biopharmaceutical sector that produces vaccines, effective treatments, and cures, at affordable costs for patients

https://www.imshealth.com/files/web/IMSH%20Institute/Reports/Global%20Medicines%20Use%20in%202020/Global%20New%20Active%20Substances%20%28NAS%29%20Available%20Since%201996.pdf

2015 Top Pharma Marketing Controversies

- Pharmaceutical re-pricing: Turing Pharmaceuticals, Buy an old drug, hike its price by 5,000%
- Insurers, pharmacy benefit managers, physicians and Presidential Candidates question pharmaceutical pricing practices and called for changes to the current system
- PBMs increase the number of drugs excluded on their formularies and get aggressive pricing with the new PCSK9 inhibitors
- Amarin sue the FDA over allegations that FDA restricted its free speech, potentially opening the door to increase off label marketing
- American Medical Association call for ban on DTC Advertising
- Pfizer's $160 b acquisition of Allergan create the world's largest drugmaker; Pfizer will move its tax domicile to Ireland

2016 Outlook

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2015 Key Issues for Pharma

Expiring patents

Shorter product life cycles

Formulary coverage challenges

Changing commercial practices
Value-based reimbursements

Pharmaceutical cost per capita
$1,010 in the US
$498 in OCDE countries

Pharma reassess strategies,

reconfigure business models, and

explore potential M&A opportunities

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2016 Outlook

1. 2016 the year of merger mania and acquisitions
2. Search is on for a drug pricing formula that is “just right.”
3. Care in the palm of your hand & Cybersecurity concerns
4. Global pharmaceutical spending could rise by 30% between 2014 and 2018 to $1.3 trillion
5. New money managers: Consumers paying higher deductibles
6. Behavioral healthcare
7. Care moves to the community
8. New databases improve patient care and consumer health
9. Biosimilars become more prevalent in the US
10. The medical cost mystery

PWC: Top health industry issues of 2016
Thriving in the New Health Economy

2016 The Year of Merger Mania

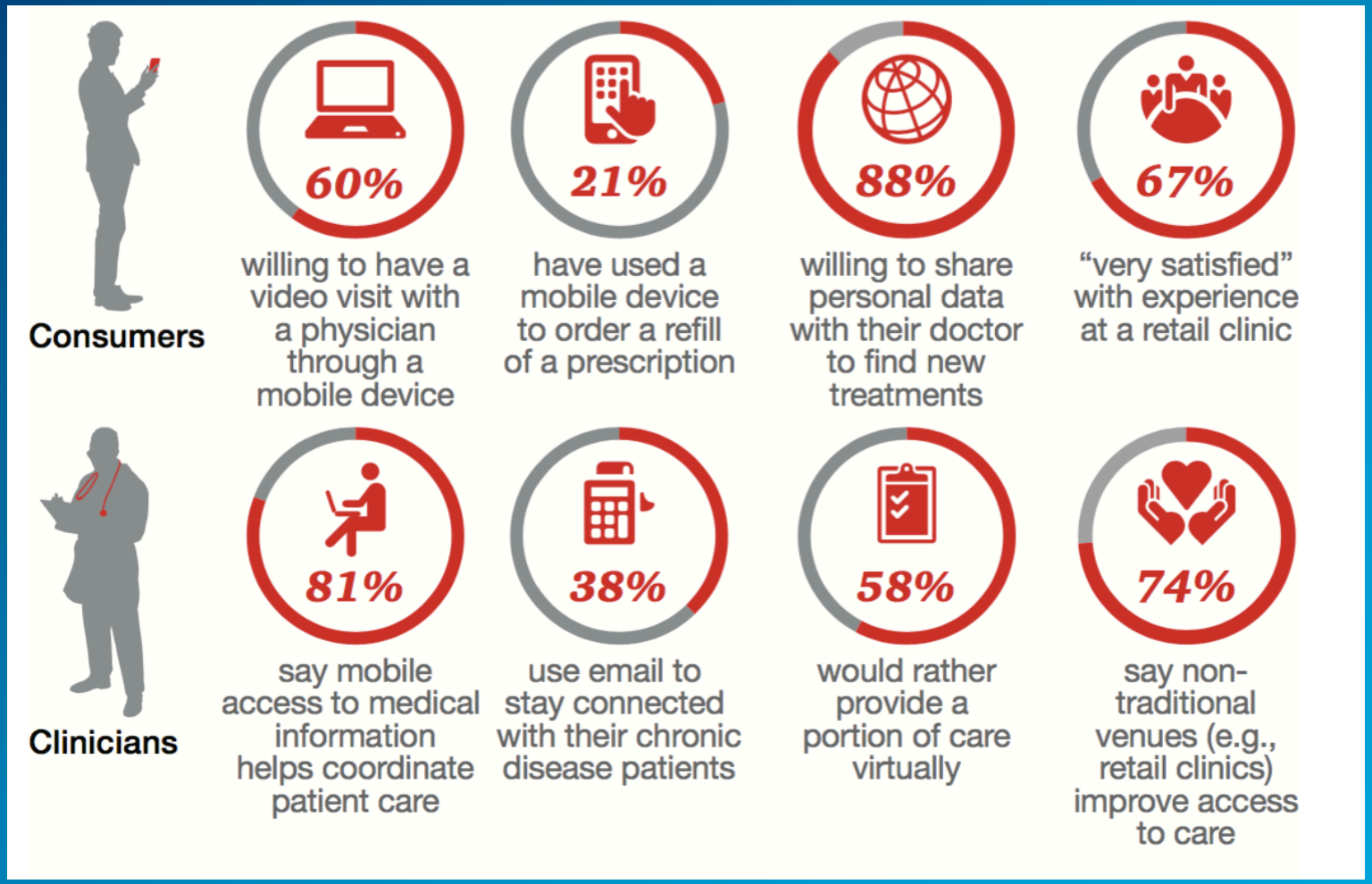
- **One Merger to End Them All!**
  - Nov 23 2015, US$160bn, Pfizer's deal to buy Allergan!
  - April 6 2016 Deal terminated after New Rules on Tax Inversions

- In 2014 68 biotechnology deals totaling US$49 billion, a 46% increase over 2013

- 17 pharmaceutical and biotechnology funding deals in 2015 totaling $449.5 million

http://www.wsj.com/articles/u-s-treasury-unveils-new-steps-to-limit-tax-inversions-1459803636

Care in the Palm of Your Hand
More Mobile, More Accessible, More Connected



Source: *HRI Consumer Survey*, PwC, 2015 and *HRI Clinician Workforce Survey*, PwC, 2014 and 2015

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Drug & Health Care Pricing

The medical cost mystery

Price the unspoken word

Percentage of consumers who have never had a conversation with a physician or nurse about

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2014 High Prices - 2015 Higher Prices

In 2014

- **Gilead** answer to Congress after placing a $1,000/day price tag on Solvadi pill for hepatitis C, then Harvoni treatment cost of $189,000
- **Vertex** Orkambi, cystic fibrosis patients $259,000 per year wholesale cost

In 2015 The 5 Most Expensive Drugs in the World

- **UniQure** 1.1 million euro price tag for Glybera
- **Soliris** $537,000
- **Naglazyme** $485,747
- **Vimizim:** $380,000
- **Elaprase:** $375,000

http://www.fool.com/investing/high-growth/2015/08/15/the-5-most-expensive-drugs-in-the-world-in-2015.aspx

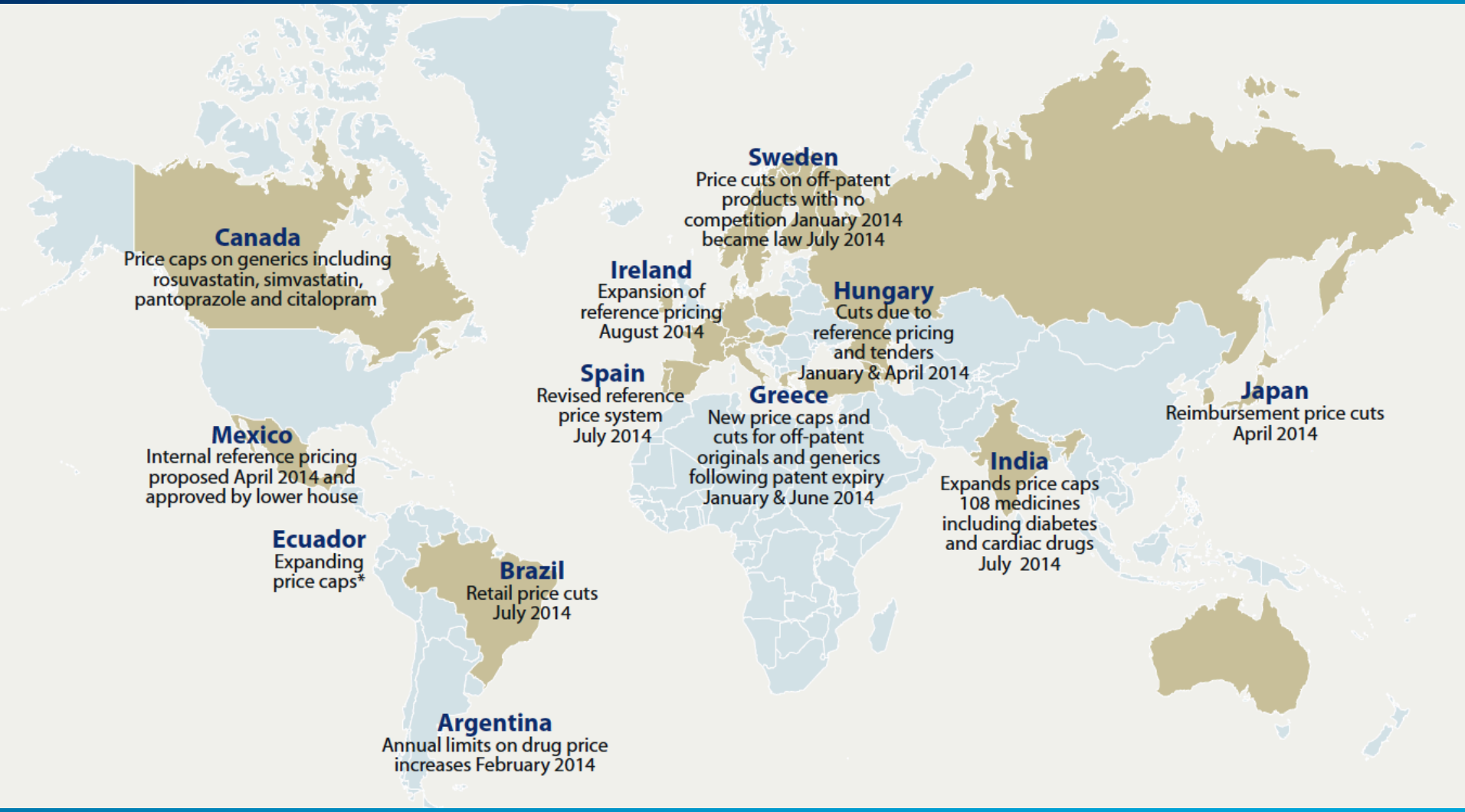
2016 US Senate Declare War on Drug Prices

- U.S. Senate Committee on Aging held hearings on drug price increases on Dec. 9, 2015
  - Senators from both parties denounced the unconscionable price increases on decades-old drugs

- Pharmaceutical industry faces twin threats:
  - First, risk of being vilified for not caring about patients, even if it launches promising life-saving drugs
  - Second, research-driven business model is under pressure from short-term investors arguing to abandon research in favor of simply acquiring drugs from start-ups

Commentary by Bill George, a senior fellow at Harvard Business School
Former Chairman & CEO, Medtronic
Previously served on the board of Novartis.

Countries Increasing Pricing Restrictions 2014



Source: IMS PharmaQuery, August 2014. Shaded countries indicate price controls - data as of Q2/2013

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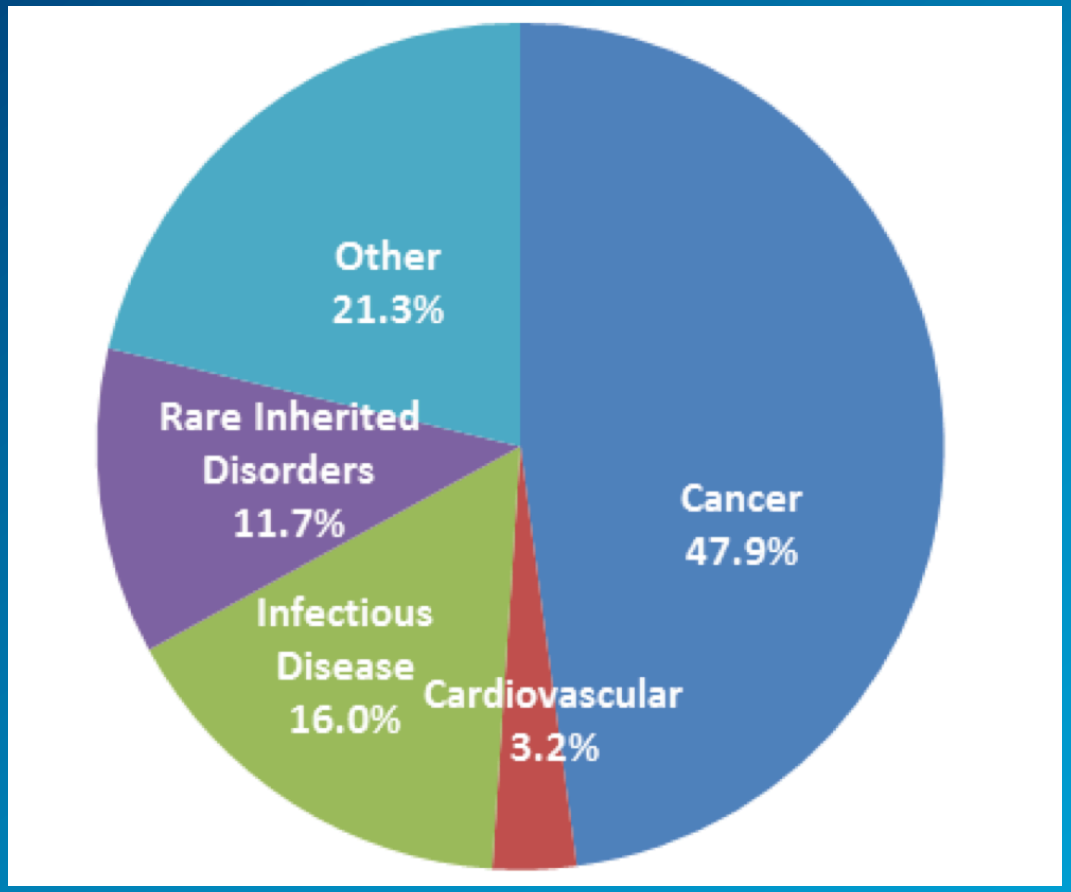
Pharma Shift To Specialty Drugs

Pharma has developed effective therapies for most prevalent diseases, high cholesterol, heart disease and diabetes

- For rare diseases cost of developing drugs is much lower
- Smaller clinical trials 100 - 200 patients vs. several thousand
- Seven years of competition-free marketing for new orphan drug
- Tax breaks on the costs of developing the drugs
- FDA to expedite reviews of innovative medicines
- FDA approves drugs designated as Breakthrough Therapies
  - 9 new drugs in 2014
  - As of December 21, 2015, FDA has given 37*,
  - 17 of them first time approvals for novel drugs

http://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm

Breakthrough Designations



A new drug may be designated as a breakthrough therapy by the FDA)

- if it is intended to treat a serious or life-threatening disease and
- Preliminary clinical evidence suggests it provides a substantial improvement over existing therapies.

Chart represents designations that have been announced by their sponsors

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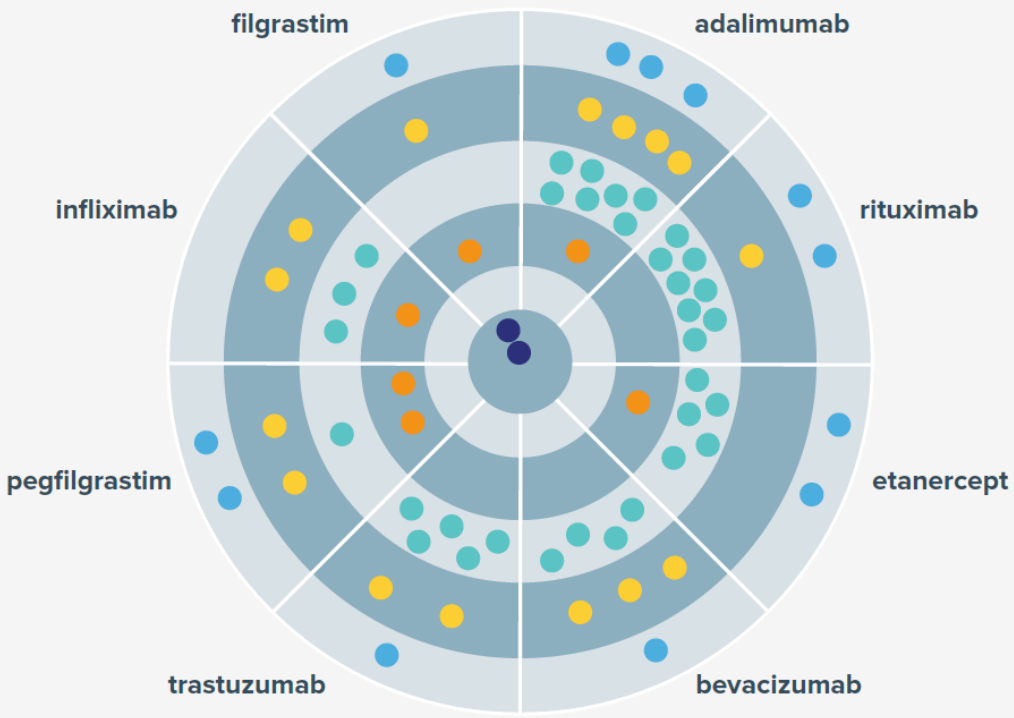
U.S. Biosimilar Pipeline for Biologics with the Greatest Number of Biosimilar Candidates

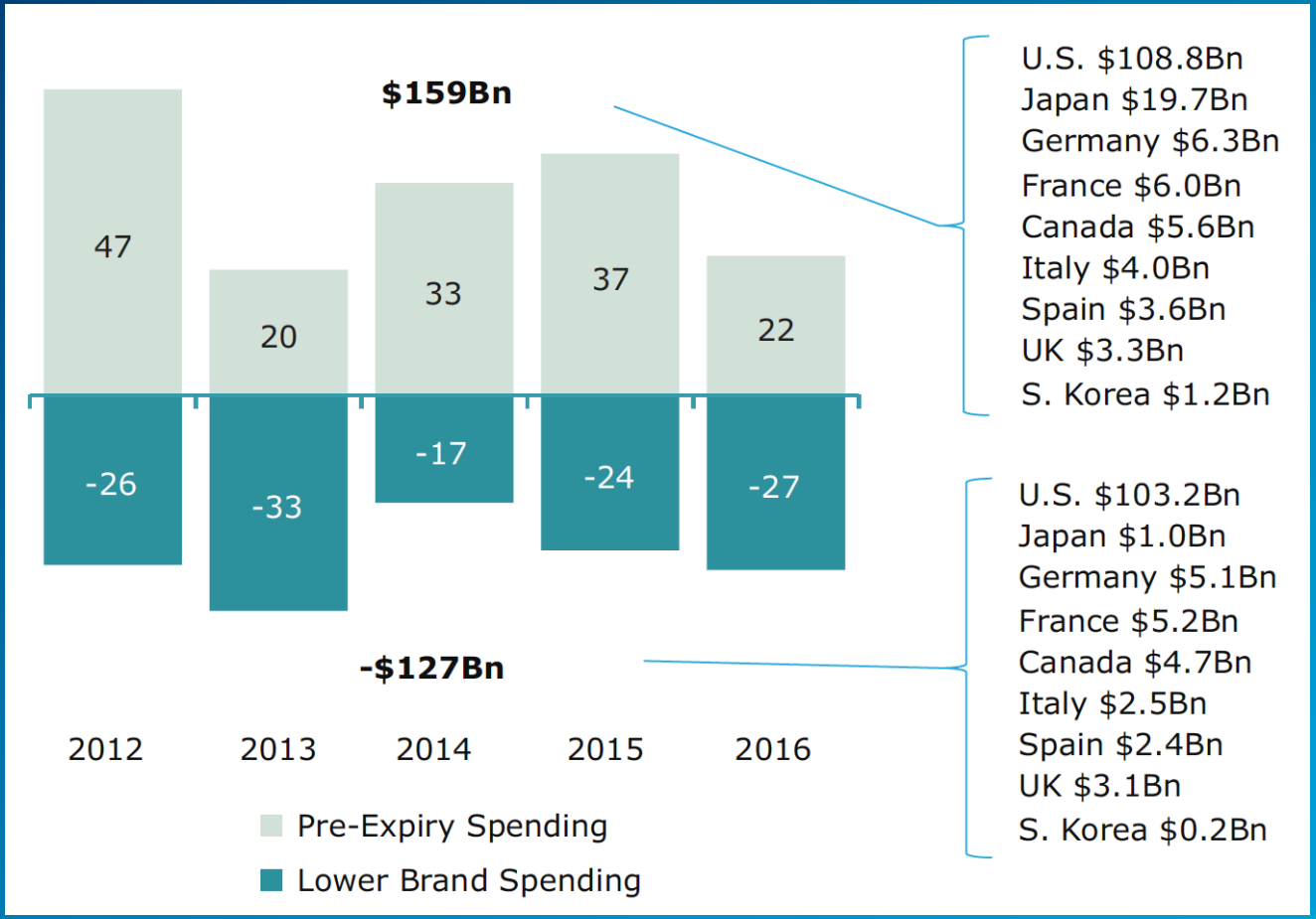


Source: IMS Health, LifeCycle R&D Focus, Dec 2015; IMS Institute for Healthcare Informatics, Mar 2016

March 2015, the first biosimilar was approved in the US via the biosimilar pathway (Zarxio filgrastim) and launched in August 2015

Global Outlook
What Will the Future Potentially Look Like?

Challenges: Patent Expiration Exposure & Impact - $127Bn



Brand Spending Shift to Generics

U.S.: $103Bn (44%) of 2011

Canada: 42% of spending will be exposed

Other Developed markets 23%

Patent expiration impact

- 13 of top 20 products
- 7 of the top 10 current leading medicines such as Lipitor®, Plavix®, Advair Diskus®, Crestor® and Nexium®

Medicines Outlook Through 2016 IMS Health
Source: IMS Institute for Healthcare Informatics, May 2012

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TALENT
The Main Engine of Business Growth

- 51% of pharmaceuticals and life sciences CEOs are worried about the availability of employees having key skills
- Consumerization dramatically changes the delivery of healthcare, old business models need to change
- 37% of pharmaceuticals and life sciences CEOs believe that creating a skilled workforce should be a government priority
- 19% believe that the government has been effective
- 64% say creating a skilled workforce is a priority for their company

Base: All respondents (Pharmaceuticals & life sciences, 119)
Source: PwC 17th Annual Global CEO Survey 2014

Patient & Payer Centric Drug Discovery & Development

Tomorrow's challenge to develop new medicines that can Prevent or Cure currently incurable diseases

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Challenges in Drug Discovery & Development

R&D productivity not improved, drug approvals have not increased significantly BUT Development Costs Escalate

- Linear: Drug R&D is conducted in a stepwise manner
- Slow: Taking a compound or molecule from early research to approved product takes over 10 years
- Inflexible: Drug development process is also very rigid and highly regulated by FDA, EMA and others
- Expensive: On average, companies spend well over US$1 billion to bring an approved drug to market
  - Includes the cost of product failures along the way
- Siloed: R&D process is highly fragmented
  - Driven by the need to protect IP
  - Fail to learn from experiences and mistakes of others

Source: Beyond borders Global biotechnology Report 2012, Ernst & Young

Key Trends Now Emerging

Trends		
Market trends	**Health and healthcare trends**	**Scientific and technological trends**
• Patients are becoming better informed • Patients are picking up a bigger share of the bill • Demand for personalised medicine is increasing • Patients want cures, not treatments • The emerging markets are becoming more important	• The burden of – and bill for – chronic disease is soaring • Healthcare payers are establishing treatment protocols • Pay-for-performance is on the rise • The boundaries between different forms of care are blurring • Financial constraints on payers are increasing	• R&D is becoming more virtualised • The research base is shifting to Asia • Remote monitoring is improving rapidly

Business Model Based on Collaborations

Implications

Pharma will need to go "beyond the medicine"

- Pharma will be paid for outcomes, not products
- Outcomes data will drive healthcare policy
- Prevention will gain a higher healthcare profile
- Pharma will need to offer "medicine-plus" packages of care
- Pharma will have to adopt more flexible pricing strategies

R&D will need to go beyond the lab

- Pharma will need access to outcomes data
- Pharma will have to work with technology vendors to virtualise R&D
- Pharma will need a wider, more multi-disciplinary skills base
- Pharma will need to expand its presence in Asia
- Pharma will need to demonstrate "real" value-for-money

The Pharma and healthcare value chains will become much more intertwined

- Pharma will have to work more closely with the regulators
- Pharma will have to collaborate with payers and providers to perform continuous trials
- Pharma will have to collaborate with numerous service providers to deliver packages of care

New Drug Development Paradigm

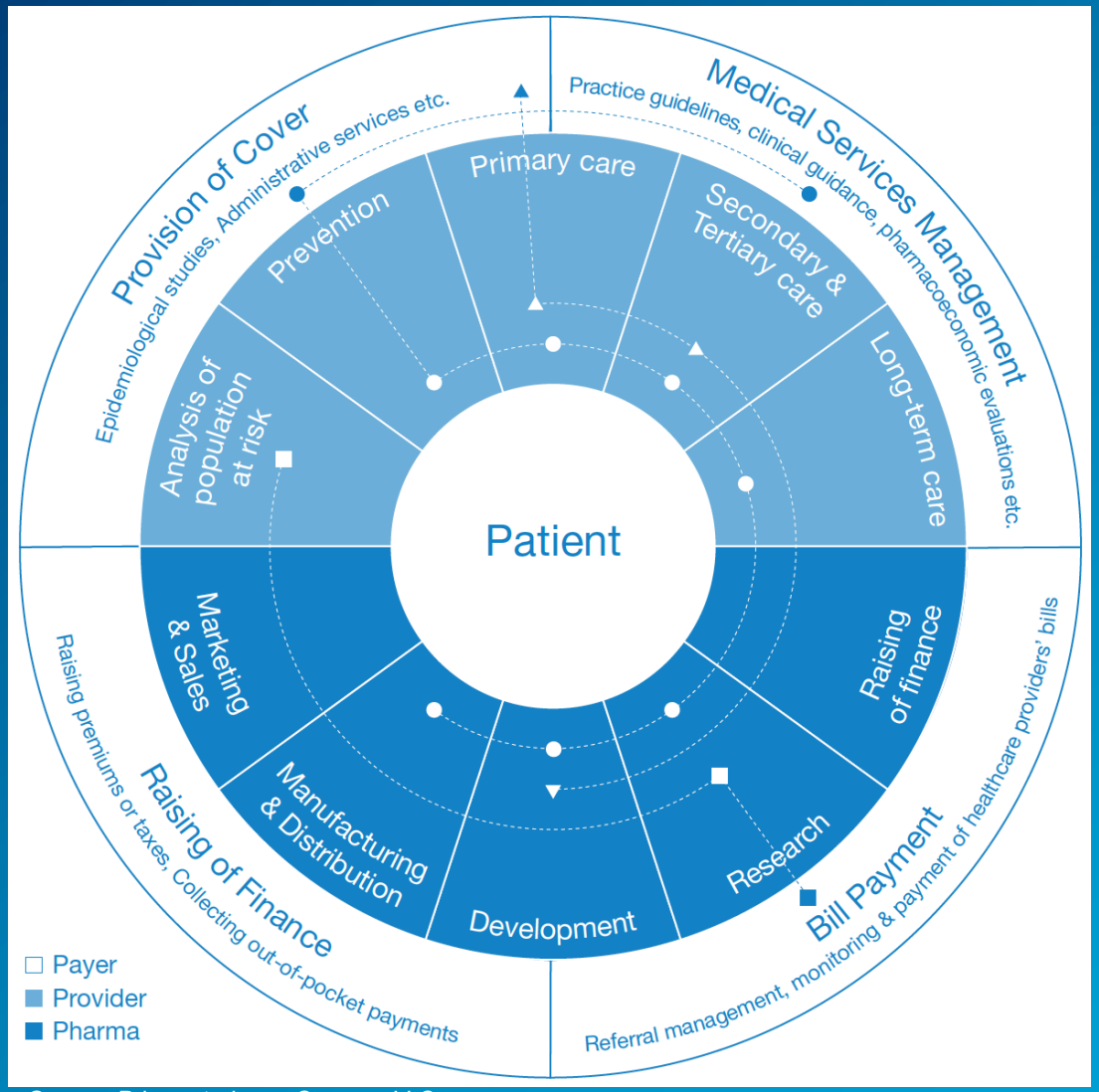
Instead of a linear, slow, inflexible, expensive & siloed drug development paradigm Pharma needs one that is iterative, fast, adaptive, cost efficient and open/networked

HOLNet approach represents a vastly different and inclusive approach to R&D

- HOLISTIC: Boundaries between drug development, product commercialization and health care delivery are blurred
- OPEN: Openness members pool their strengths and assets. Involve sharing any resulting output e.g., creating open standards, making insights available to all members and often to nonmembers as well
- LEARNING: Learning rapidly, in real time, by connecting data from across the ecosystem. Adjust approaches from clinical trials to standards of care saving time and money and potentially increasing success rates
- NETWORK: Radically reinventing R&D and unleashing the transformative potential of big data requires the participation of diverse players from across the ecosystem

Source: Beyond borders Global biotechnology Report 2012, Ernst & Young
http://onlinelibrary.wiley.com/doi/10.1002/cpt.59/pdf

Convergence of Value Chain
Single Circular Value Chain: The Patient



- Providers depends on
  - Revenues payers raise
  - Medicines from Pharma
- Pharma depends on
  - Access to the patients
  - Income from payers
- Relationship between different players is often quite antagonistic and, while they continue to clash, they are struggling to retain their respective goals

Source: PricewaterhouseCoopers LLC
http://www.pwc.com/gx/en/pharma-life-sciences/pharma2020/vision-to-decision.jhtml

Sustainable Business

In order to have a sustainable business pharma need to continue to innovate

Innovation!

- Disruptive innovation:
  - CURE or PREVENT the disease & reduce mortality or morbidity
- Incremental innovation
  - Reduce the cost of care
  - Improve the quality of life
  - Safer or easier to use
  - Improve patient compliance
- Issue “ME TOO” drugs
  - Drugs with same mode of action
  - Maybe the third or fourth market entrant may be superior!
- Payers are not going to pay a premium unless
  - Drug shows disruptive innovation
  - Demonstrate clear superiority in comparative trials with pharmacoeconomic benefits

Formula for Successful Innovation

1. Identify areas to play

=

Diversification from key TA expertise is complementary & focussed like fastest growing

+

Innovation is focussed in high return therapy areas

2. R & D

=

R&D process is designed cost-effectively to allow balanced emerging/ mature NCE sales by enabling volume play

+

R&D process is shared and de-risked through partnerships and alliances

3. Identify un-met need

=

Identifiable patient population for whom treatment will work

+

Payers agree with targeted unmet need

+

Appropriate outcomes data collected and firm plan for RWE

1. Focus
2. Nimble and Flexible
3. Partnerships
4. Expending geographic footprint

FDA Rewards Innovation

Fast Track

Fast track is a process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.
Fast Track

Breakthrough Therapy

A process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.
Breakthrough Therapy

Accelerated Approval

These regulations allowed drugs for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint.
Accelerated Approval

Priority Review

A Priority Review designation means FDA's goal is to take action on an application within 6 months.
Priority Review

http://www.fda.gov/forpatients/approvals/fast/ucm20041766.htm

FDA developed 4 distinct approaches to making drug treating serious diseases available as rapidly as possible:

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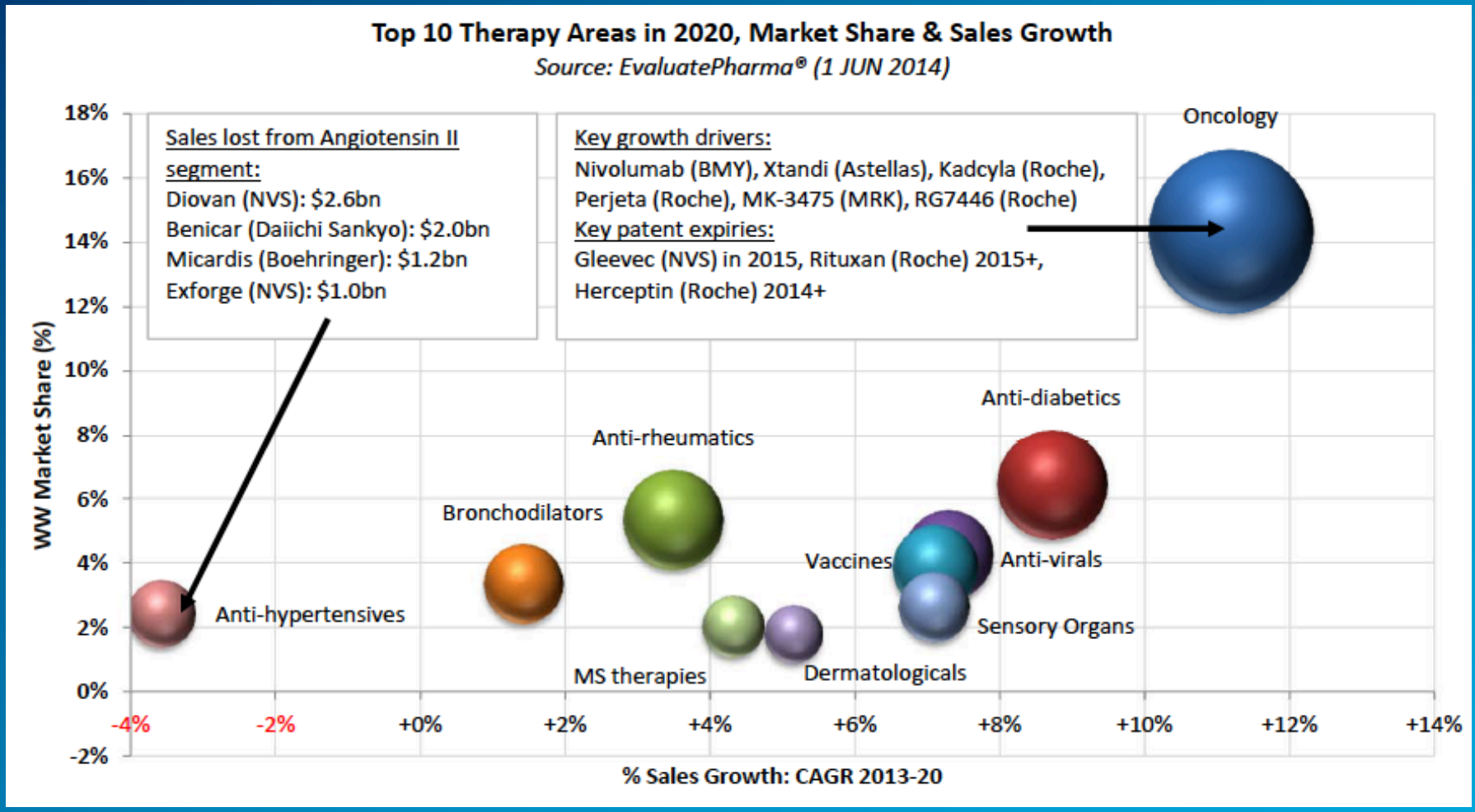
Oncology Largest & Fastest Growing Segment



Source: Worldwide Prescription Drug & OTC Sales by EvaluatePharma® Therapy Area (2013 & 2020

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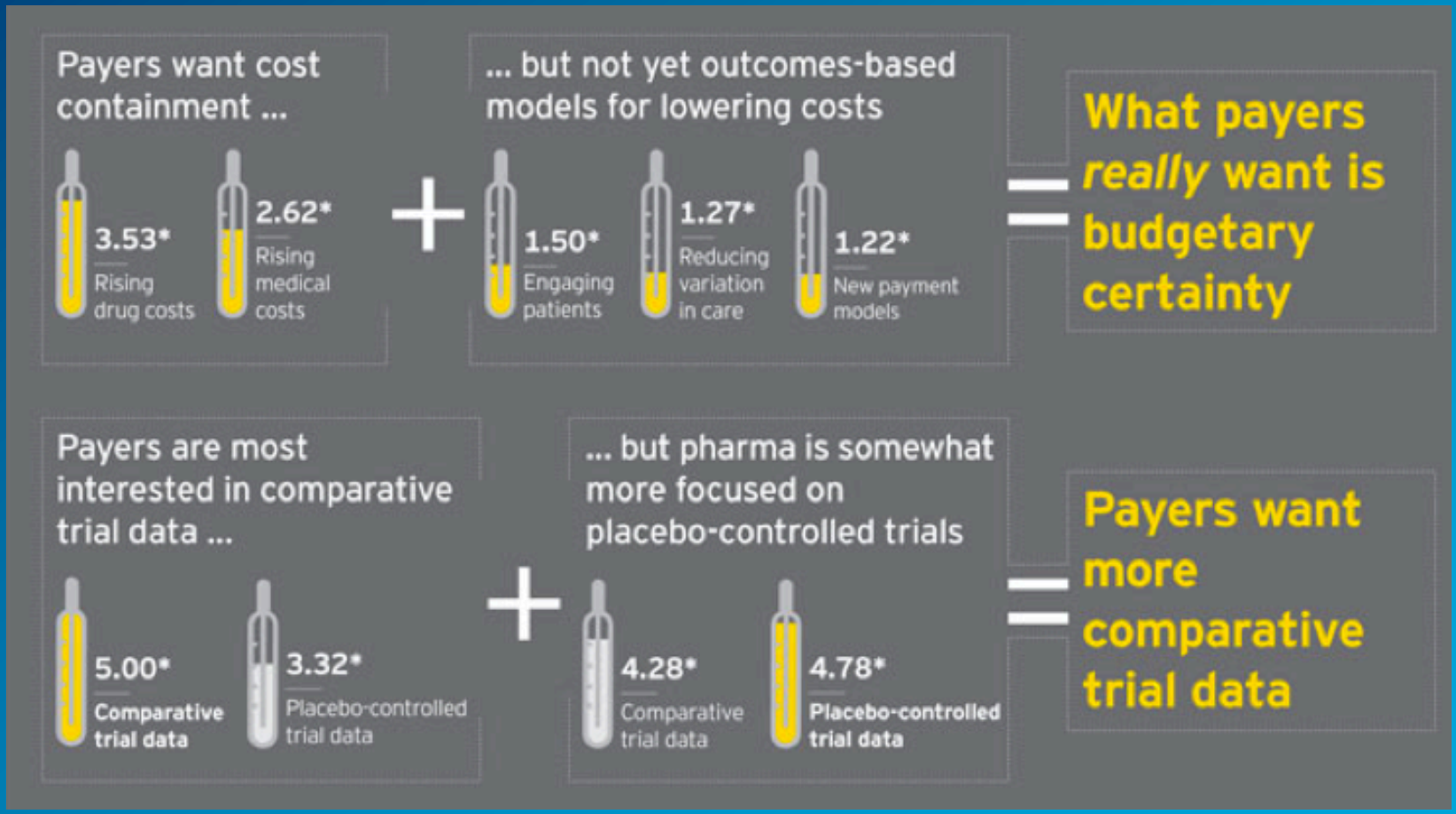
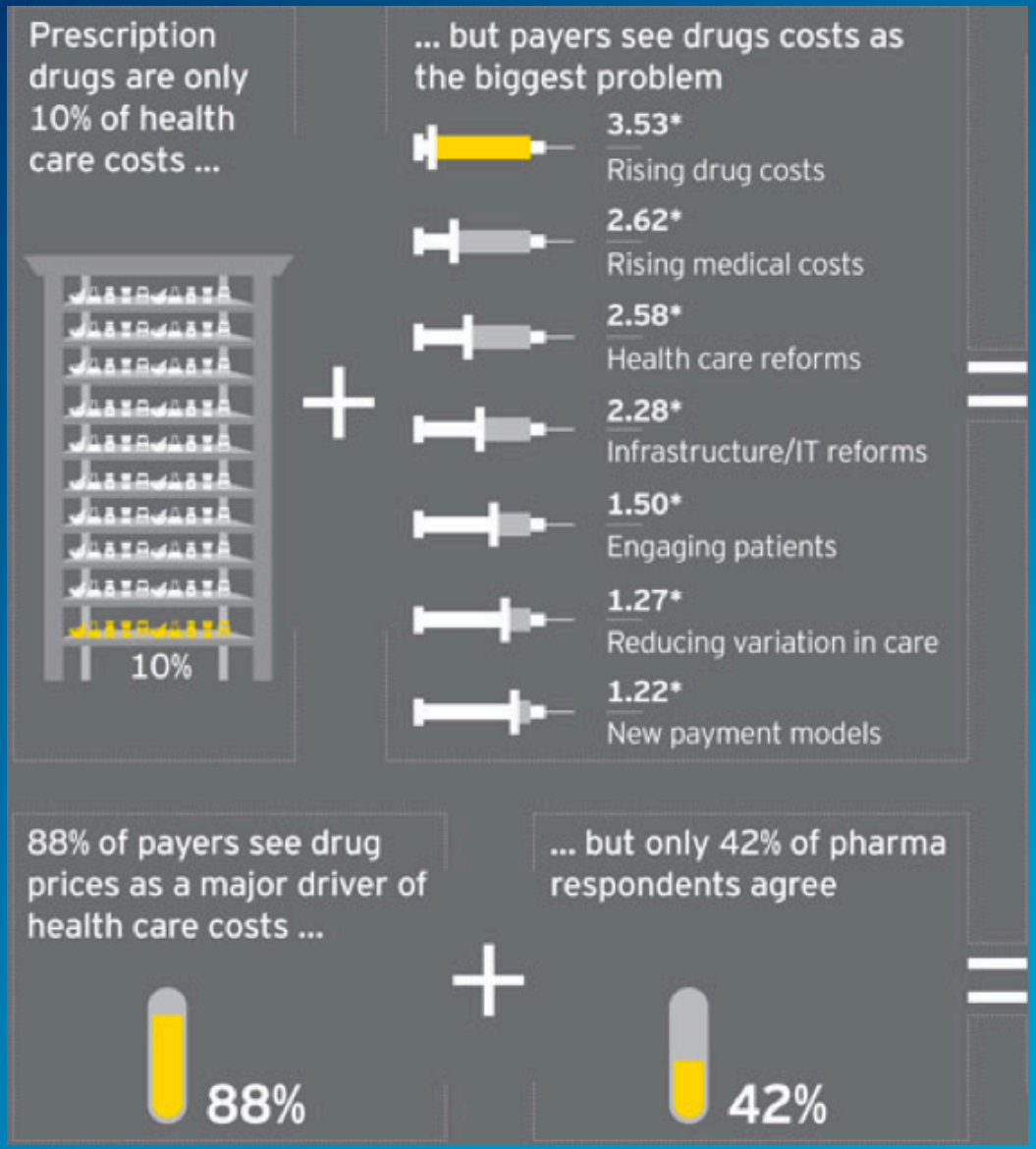
The Rise of the Payers

They Decide Which Product to Rx



Source: EY Progressions 2014 Payer Survey

PRICE Perception Issue



Pharma has a perception problem

Source: EY Progressions 2014 Payer Survey

References & Additional Reports

- http://www.imshealth.com/en/thought-leadership/ims-institute/reports
- http://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-healthcare-and-life-sciences-predictions-2020.pdf
- http://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-lshc-2015-health-care-outlook-global.pdf
- http://www2.deloitte.com/content/dam/Deloitte/global/Documents/Life-Sciences-Health-Care/gx-uk-measuring-the-return-from-pharmaceutical-innovation-2014.pdf
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- http://www.mckinsey.com/insights/health_systems_and_services/pharmas_first_to_market_advantage
- http://cmr.thomsonreuters.com/pdf/cmr-fb-exec-2014.pdf
- http://images.info.science.thomsonreuters.biz/Web/ThomsonReutersScience/%7B82a68aff-4de4-48ca-a0ea-f4a7cc4b3b98%7D_Eat_or_Be_Eaten_The_Specialty_Pharma_Survival_Story_.pdf
- http://images.info.science.thomsonreuters.biz/Web/ThomsonReutersScience/%7B0599f9d0-1a68-4cde-a0bb-215b11f4a848%7D_Venture_Financing_Trends_and_M_A.pdf
- http://cmr.thomsonreuters.com/services/factbook/
- http://www.ey.com/Publication/vwLUAssets/EY-beyond-borders-unlocking-value/$FILE/EY-beyond-borders-unlocking-value.pdf
- http://www.ey.com/Publication/vwLUAssets/ey-new-horizons-health-care-industry-report-2014/$FILE/ey-new-horizons-health-care-industry-report-2014.pdf
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- http://www.ey.com/Publication/vwLUAssets/EY_-_Progressions_2014:_Navigating_the_payer_landscape/$FILE/EY-progressions-2014.pdf
- http://www.ey.com/Publication/vwLUAssets/EY-global-corporate-divestment-study-life-sciences/$FILE/EY-global-corporate-divestment-study-life-sciences.pdf
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- http://www.ey.com/Publication/vwLUAssets/EY-invivo/$File/EY-invivo.pdf
- http://www.ey.com/DLResults?Query=[CountryCode]=GL~[LanguageCode]=en~[T_Industry]=%28Industries\Life%20Sciences%29
- http://www.pwc.com/gx/en/healthcare/publications/index.jhtml
- http://www.pwc.com/en_US/us/health-industries/publications/assets/pwc-moneytree-biotechnology-medical-devices-q4-2014.pdf
- http://pwchealth.com/cgi-local/hregister.cgi/reg/pwc-hri-pharma-fda.pdf
- http://www.pwc.com/en_US/us/health-industries/pharma-life-sciences/publications/assets/pwc-chi-california-biomedical-industry-report-2015.pdf
- http://pwchealth.com/cgi-local/hregister.cgi/reg/pwc-hri-aca-five-year-anniversary.pdf
- http://pwchealth.com/cgi-local/hregister.cgi/reg/pwc-rx-marketplace-quarterly-issue-5.pdf
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- http://www.imap.com/local/media/article_documents/IMAP_Pharma_Report_2015_6C84003C2573C.pdf
- http://media.mmm-online.com/documents/119/pharma_report_2015_29732.pdf
- http://www.fiercepharma.com/special-reports/top-10-patent-expirations-2015
- http://info.evaluategroup.com/rs/evaluatepharmaltd/images/EP240614.pdf
- http://www.phrma.org/sites/default/files/pdf/2015_phrma_profile.pdf
- http://www.eiu.com/public/topical_report.aspx?campaignid=Industries2015
- http://www.fiercebiotech.com/story/top-5-trends-biotech-2015/2014-12-24
- http://www.genengnews.com/insight-and-intelligence/top-ten-bioindustry-trends-for-2015/77900323/
- https://www.jpmorgan.com/cm/BlobServer/2015-healthcare-01.pdf?blobkey=id&blobwhere=1320662161195&blobheader=application/pdf&blobheadername1=Cache-Control&blobheadervalue1=private&blobcol=urldata&blobtable=MungoBlobs
- http://kff.org/report-section/ehbs-2015-summary-of-findings/

Thank you

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