Globalization of Drug Development : Stipulation and Perceptibility

Dr Deven V Parmar MD,FCP

Agenda

- Overview
- Regulatory Perspective
- Global trends in Drug Development/ Clinical trials
- Global Opportunities
- Global Challenges

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INTERNATIONAL BESTSELLER

NOBEL PRIZE–WINNING AUTHOR OF
GLOBALIZATION AND ITS DISCONTENTS

MAKING GLOBALIZATION WORK

JOSEPH E. STIGLITZ

WITH A NEW AFTERWORD

"A brave book. . . . Stiglitz does an excellent job of describing dense topics . . . in language that's understandable and accessible."
—Russ Juskalian, *USA Today*

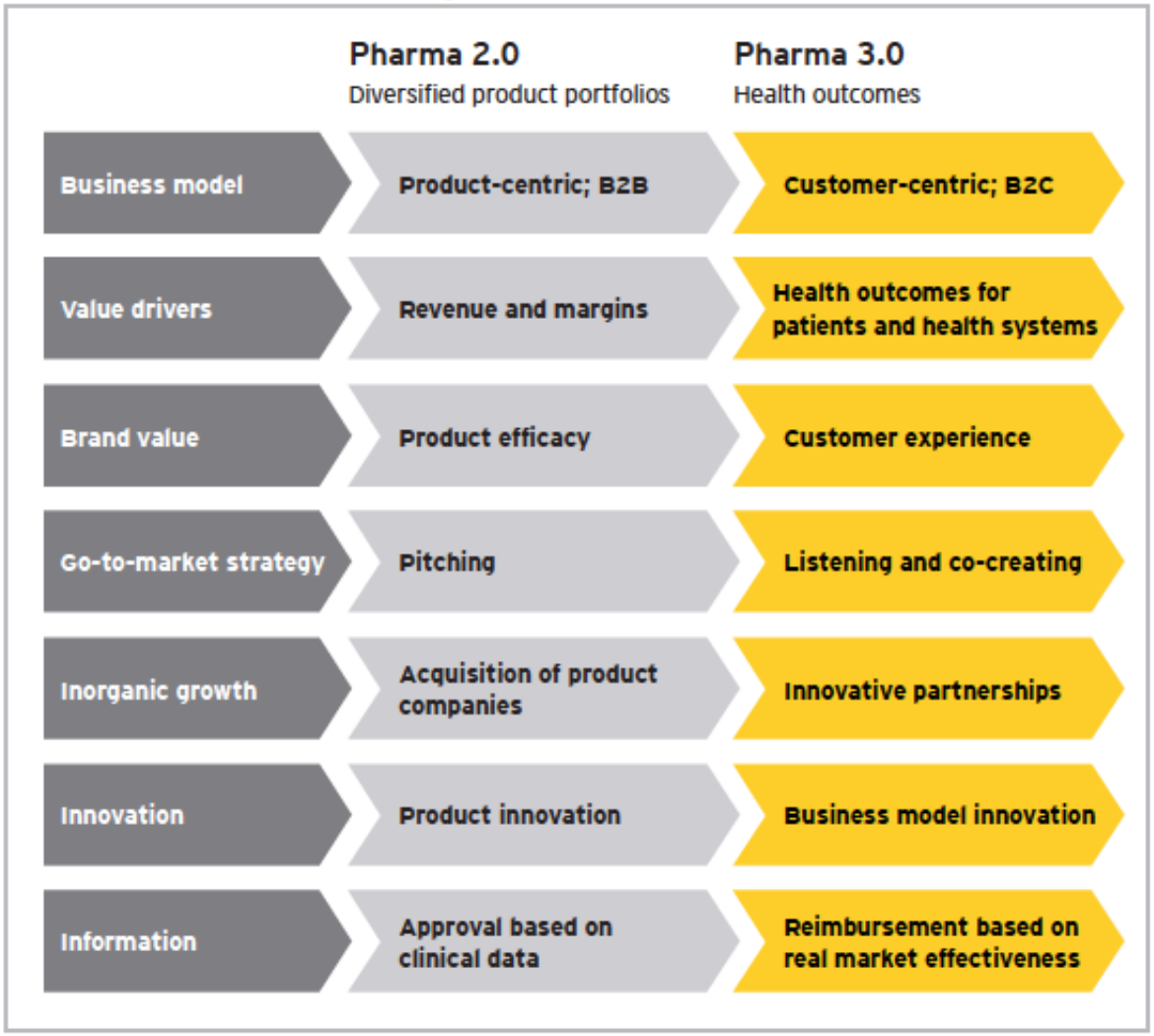
Globalization Works?

- Many economist & world leaders agree that globalization is supposed to create higher living standards, increased access to foreign markets, investments & open borders.
- However, according to JS, globalization is desperately failing the 80% of the world's population living in developing countries & 40% that lives in poverty.

The Third Place: HealthCare Everywhere

- Health Care Cost are becoming unsustainable, in large part due to chronic disease epidemic fueled by unhealthy lifestyles, aging populations & increasing standards of living.
- Health Care will become more patient centric & ubiquitous – delivered wherever the patient happens to be.
- Patients who have grown increasing comfortable with empowering technologies are taking more active roles in managing their health & are demanding a different model in the third place.

Pharma 3.0: the shift from products to health outcomes



Source: Ernst & Young.

Move to evidence based, outcomes focused, behavior driven world

Progressions : Global Life Sciences, E & Y, 2012

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Regulatory Perspective

The United States imports:

80 percent of active pharmaceutical ingredients

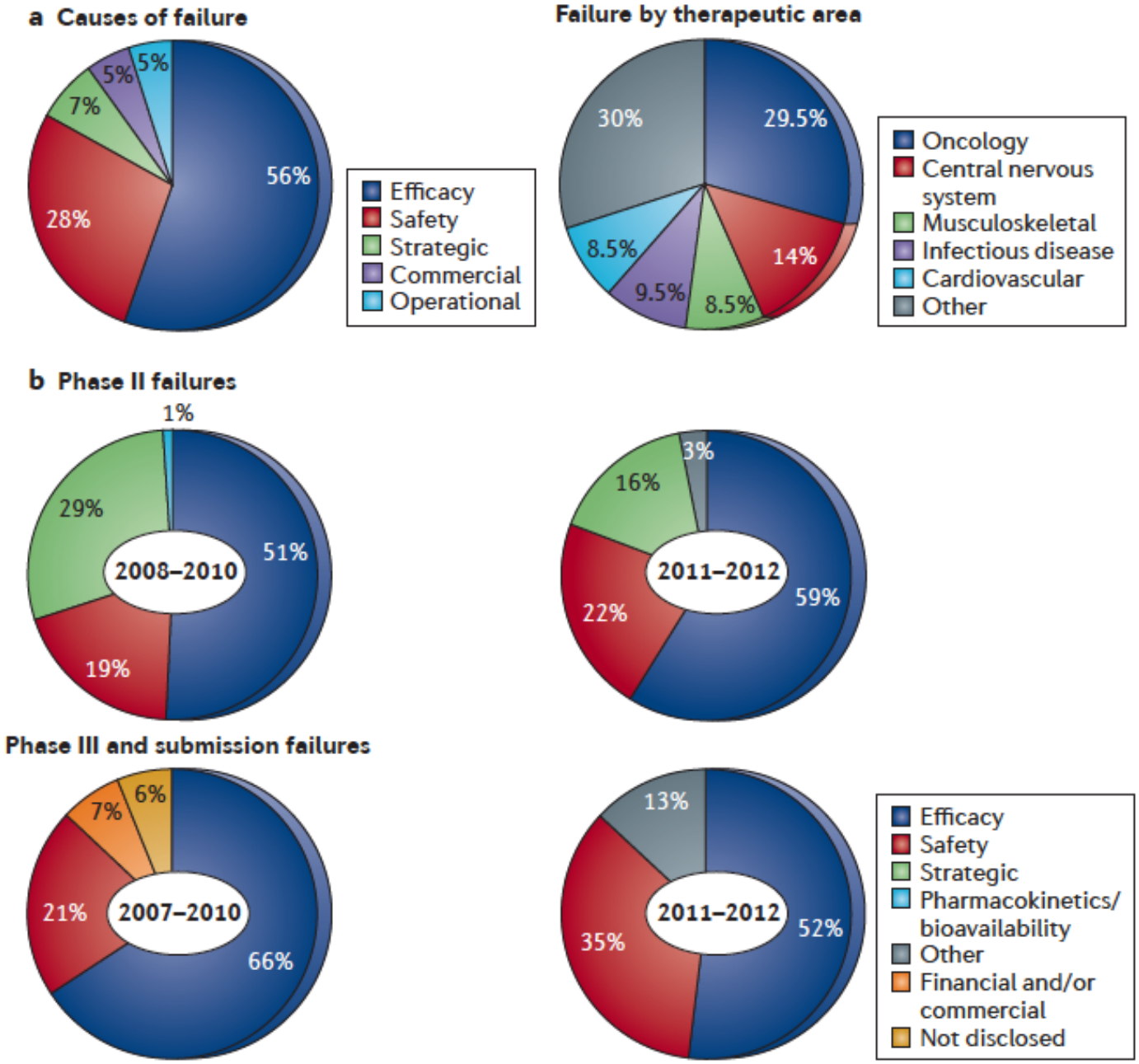
80 percent of seafood

40 percent of finished dosage drugs

Approximately 50 percent of fresh fruit

Approximately 20 percent of fresh vegetables

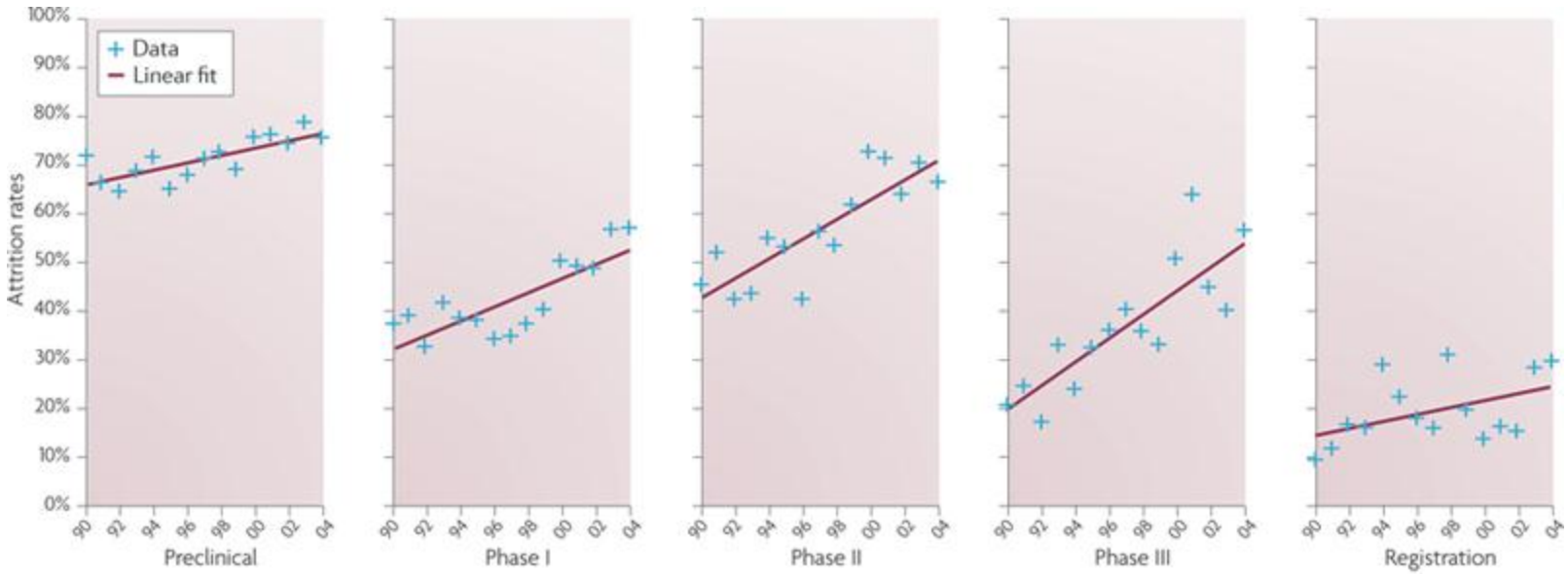
Sources: Hamburg, M. 2011. *Food and Drugs: Can Safety Be Ensured In a Time of Increased Globalization?* Presented at the Council of Foreign Relations New York Symposium, January 31.



Trends in Attrition

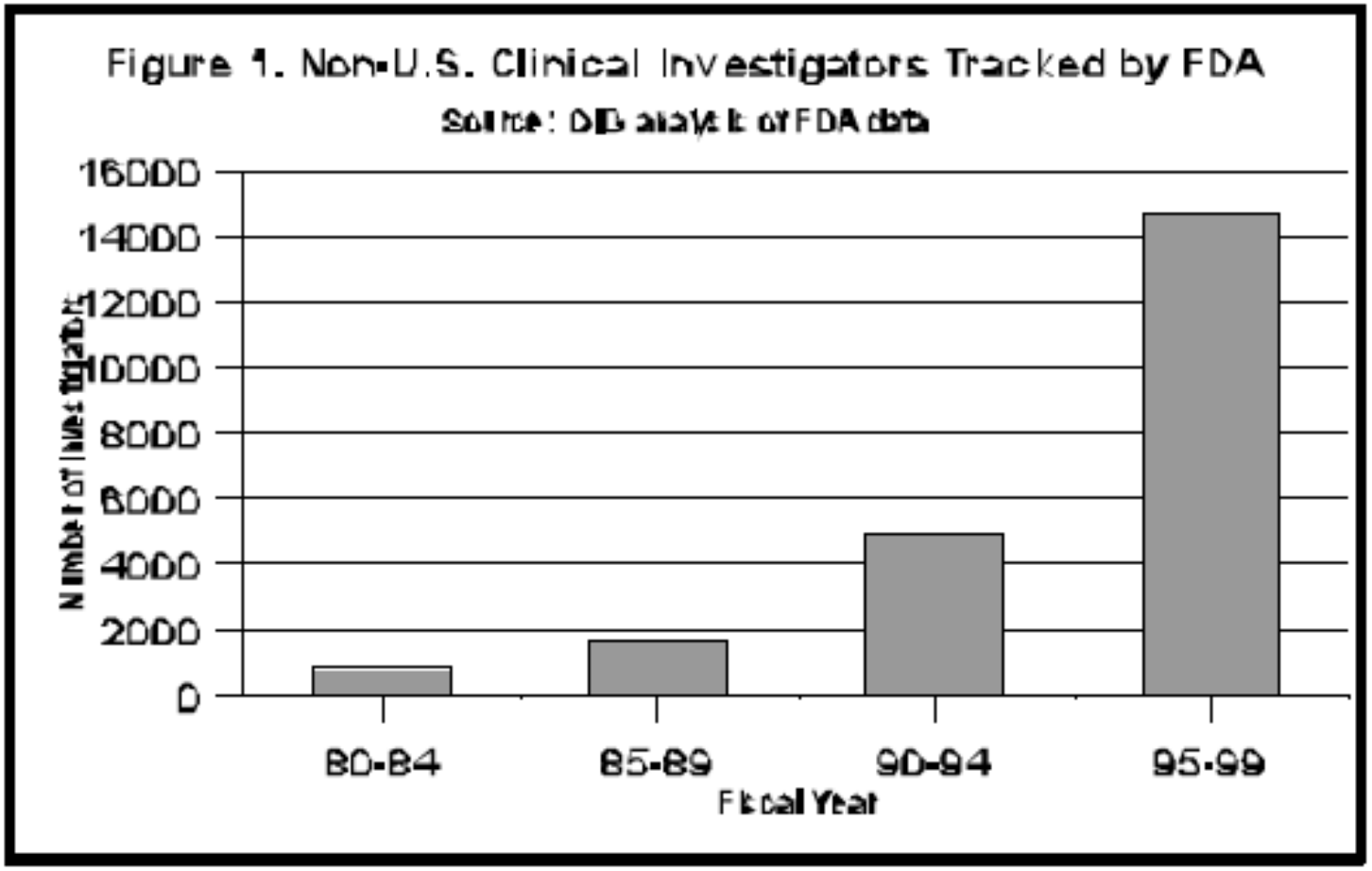
Source: Nature June 2011

Cont'd…

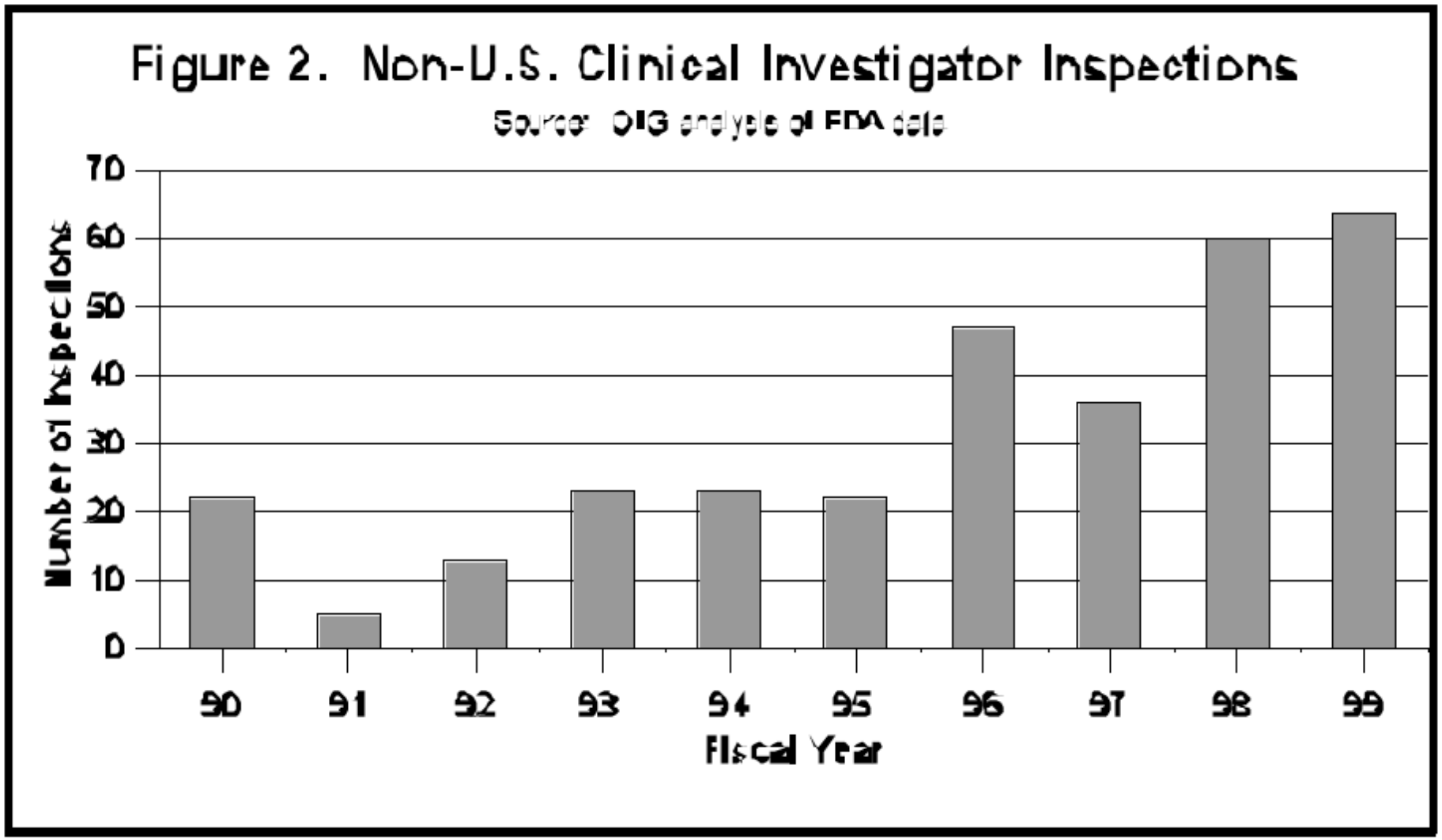


Source: Nature June 2011

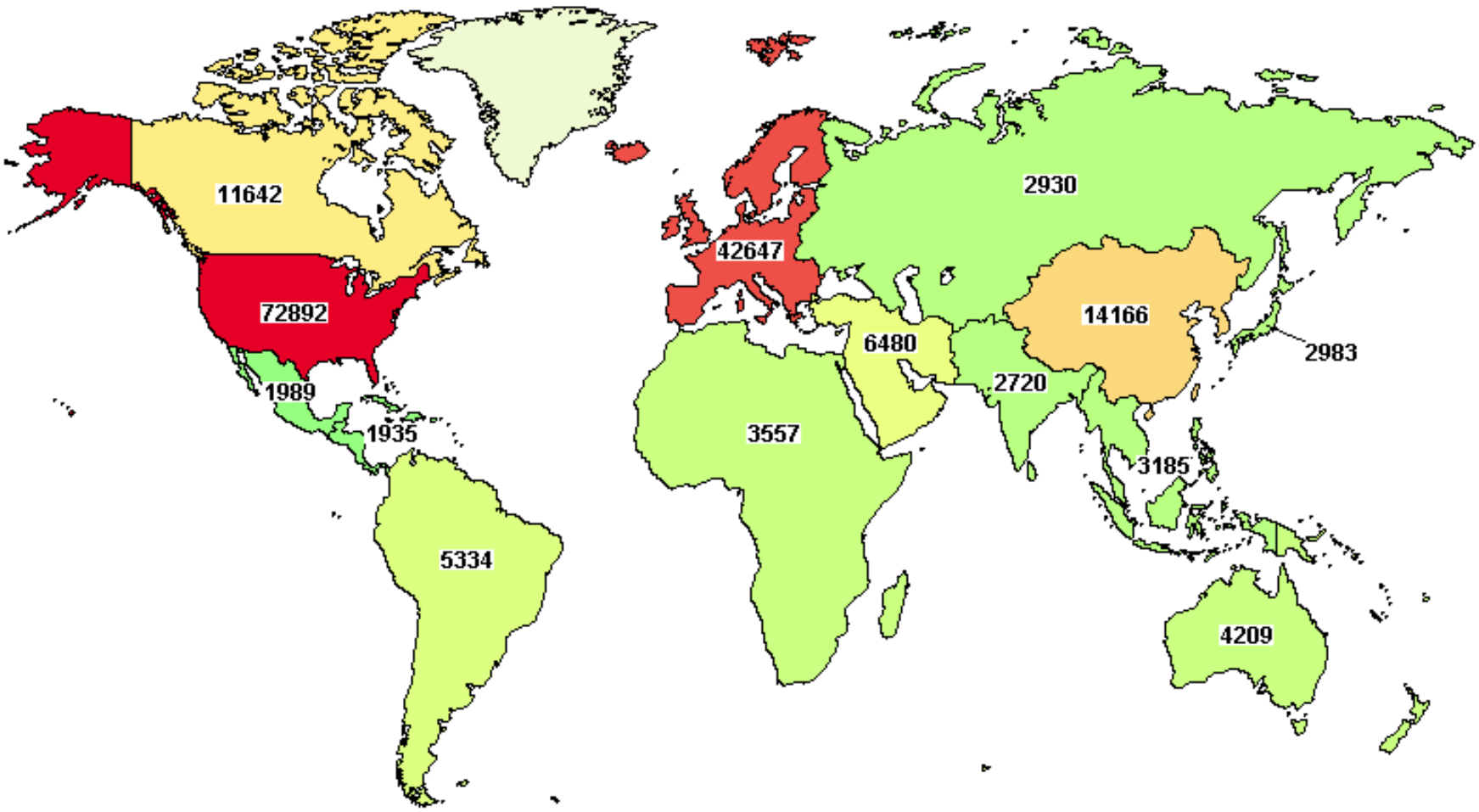
IND application increased 16 fold…



Source: FDA : Globalization of Clinical Trials, 2001

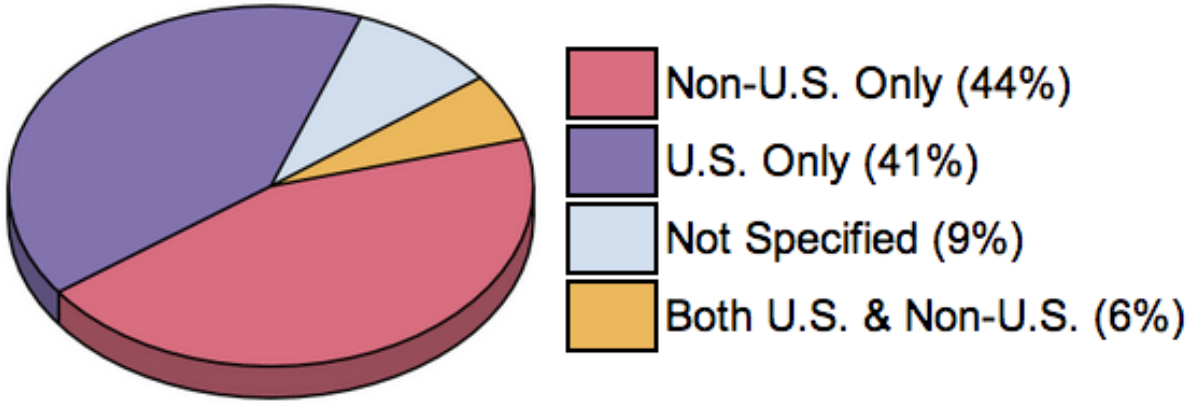


Source: FDA : Globalization of Clinical Trials, 2001



Accessed on 22nd Nov, 2013 Clinical trial.gov

Location of Registered Studies



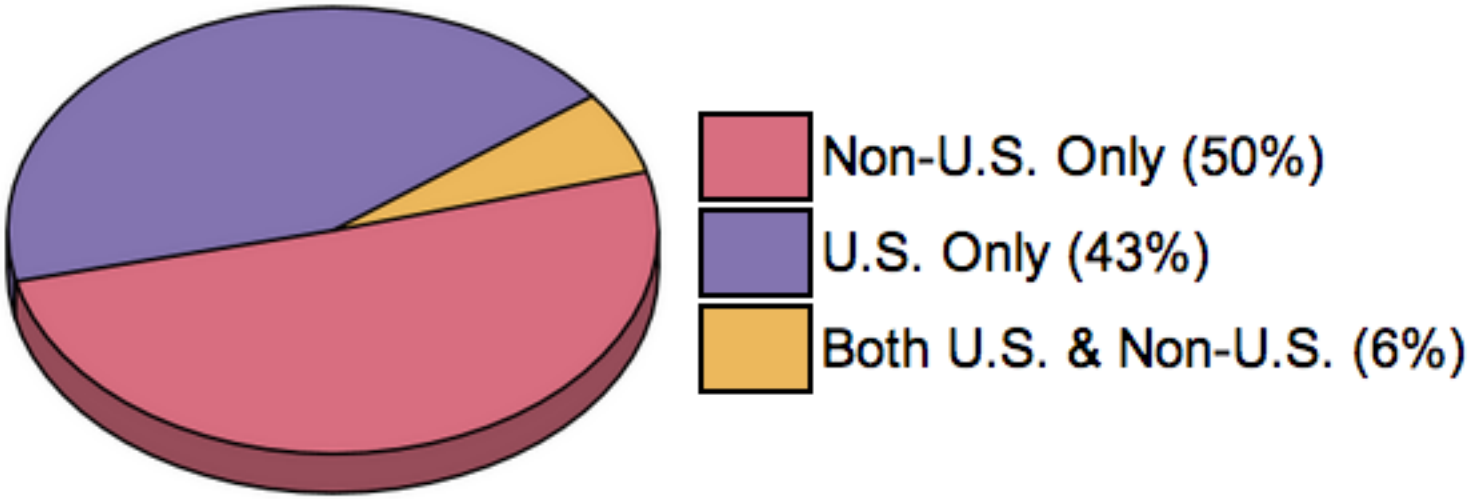
Location	Number of Registered Studies and Percentage of Total
Non-U.S. Only	68,855 (44%)
U.S. Only	63,210 (41%)
Not Specified*	14,043 (9%)
Both U.S. & Non-U.S.	9,682 (6%)
Total	155,790

* Not Specified: The location of the study was not provided by the Sponsor.

(Data as of November 22, 2013)

Accessed on 22nd Nov, 2013 Clinical trial.gov

Location of Recruiting Studies



Location	Number of Recruiting Studies and Percentage of Total
Non-U.S. Only	15,937 (50%)
U.S. Only	13,702 (43%)
Both U.S. & Non-U.S.	1,948 (6%)
Total	31,587

(Data as of November 22, 2013)

Accessed on 22nd Nov, 2013 Clinical trial.gov

Guidance for Industry and FDA Staff

FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND

Frequently Asked Questions

Additional copies are available from:
Division of Drug Information, WO51-2201
Office of Communication
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993-002
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
Email: DRUGINFO@fda.hhs.gov
(Tel) 301-796-3400; (Fax): 301-847-8714
and/or
Office of Communication, Outreach and Development, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm
Email: ocod@fda.hhs.gov
(Tel) 800-835-4709 or 301-827-1800
and/or
Office of Good Clinical Practice
Office of the Commissioner
http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Center for Biologics Evaluation and Research
Office of Good Clinical Practice
March 2012

To Do List for a Regulator…

- Nature of the challenge
- Improving the efficiency of development through collaboration and communication
- Improving internal FDA processes to support new paradigms
- Staying open to change

Douglas C. Throckmorton, Deputy Director for Regulatory Programs, CDER, FDA DIA April 18, 2012

Regulatory Science Activities: Communication

- Provide clear roadmap to speed development
  - Guidances: Adaptive Trial Designs, Meta-Analysis, Adverse Events Reporting Rule
  - Drug Development Tools:
    - PROs, Biomarkers, Animal Models (CT)
  - PDUFA V proposal for enhanced communications teams to aide drug developers

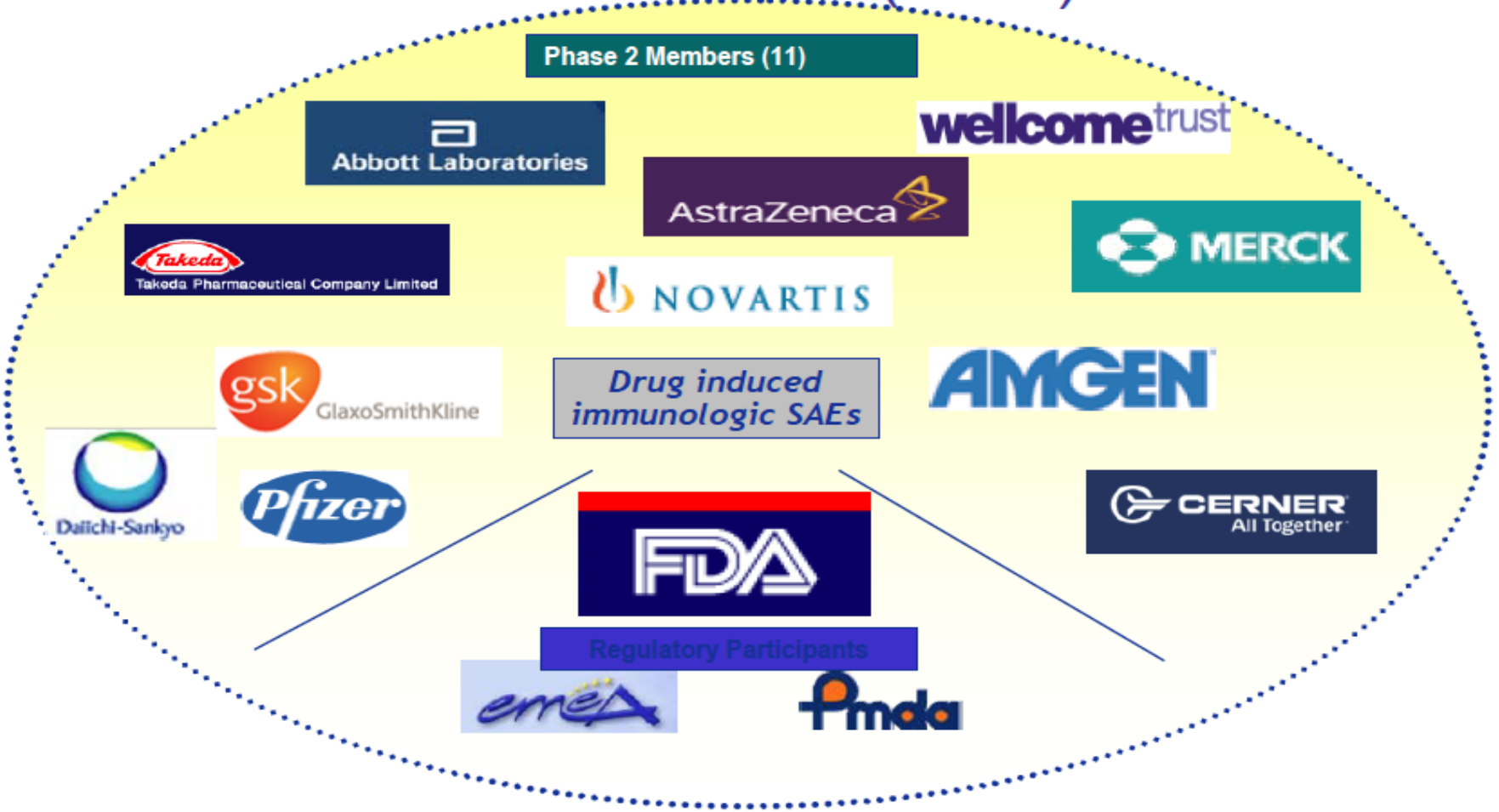
Douglas C. Throckmorton, Deputy Director for Regulatory Programs, CDER, FDA DIA April 18, 2012

Example of Regulatory Innovation: Adaptive Trial Design Guidance

- Adaptive Design Clinical Trials for Drugs and Biologics (2010)
- Goals:
  - Decrease time between discovery & "confirmatory" studies
  - Make studies more likely to succeed by adapting design elements that could not be fully known when the study was planned and powered:
    - effect size
    - event rate in the population
    - most responsive subset
    - the right dose
    - the best study endpoint

Douglas C. Throckmorton, Deputy Director for Regulatory Programs, CDER, FDA DIA April 18, 2012

International Serious Adverse Event Consortium (iAES)



Douglas C. Throckmorton, Deputy Director for Regulatory Programs, CDER, FDA DIA April 18, 2012

Example: International Serious Adverse Event Consortium (iAES)

- Matching phenotyped cases and controls for pharmacogenetic research on important drug-induced SAEs: TdP, Liver toxicity, Allergic Reactions
- Developing effective whole genome genotyping and sequencing methods for SAE research
- Supporting the development of the computational methods necessary for effective GWAS analysis (both genotyping and sequencing)
- Creating a timely and publicly available scientific "databank"(raw data and genetic markers) associated with key drug-induced SAEs
- Managing the intellectual property related to genetic markers associated with SAEs, to ensure broad and open access to all users in all settings
- Initiated in concert with FDA as part of Critical Path Initiative

Douglas C. Throckmorton, Deputy Director for Regulatory Programs, CDER, FDA DIA April 18, 2012

EMA & FDA Initiative

European Medicines Agency

US Food and Drug Administration

London, 29 July 2009
Doc. Ref. EMEA/INS/GCP/538414/2008
FDA Mod. 20 August 2009

EMEA-FDA GCP Initiative

Terms of engagement and procedures for participating authorities

Pilot Phase (18 months): Start date 01 September 2009

EMA & FDA Initiative

2. Objectives

2.1 To Conduct Periodic Information Exchanges on GCP-Related Activities

a. To streamline the sharing of information relevant to GCP inspection planning so that the selection of studies and sites is well informed, and inspection coverage is improved.

b. To exchange GCP-related information contained in applications for scientific advice, orphan medicines designation, pediatric investigational plans, marketing authorization or post-authorization activities of significant public health interest.

c. To communicate effectively and in a timely manner on inspection outcomes (negative and positive) and their potential impact, where the clinical trials and/or inspected sites/organizations are of common interest.

2.2 To Conduct Collaborative GCP Inspections

a. To build mutual understanding of, and confidence in, the GCP inspection processes utilized by the EU/EMEA and FDA – through the sharing of information, experience and inspection procedures, and cooperation in the conduct of inspections.

b. To improve effectiveness of inspections by sharing best-practice knowledge in order to enhance inspection techniques and processes.

2.3 To Share Information on Interpretation of GCP

a. To keep each other informed of GCP-related legislation, regulatory guidance documents, position papers, and policy documents that might be in draft or finalized form.

b. To identify and act on areas where greater convergence could be achieved to the benefit of the clinical research process.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 April 2012
EMA/121340/2011
The European Medicines Agency Working Group on Clinical Trials conducted outside of the EU/EEA

Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities

Cont'd…

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Key 2016 Numbers

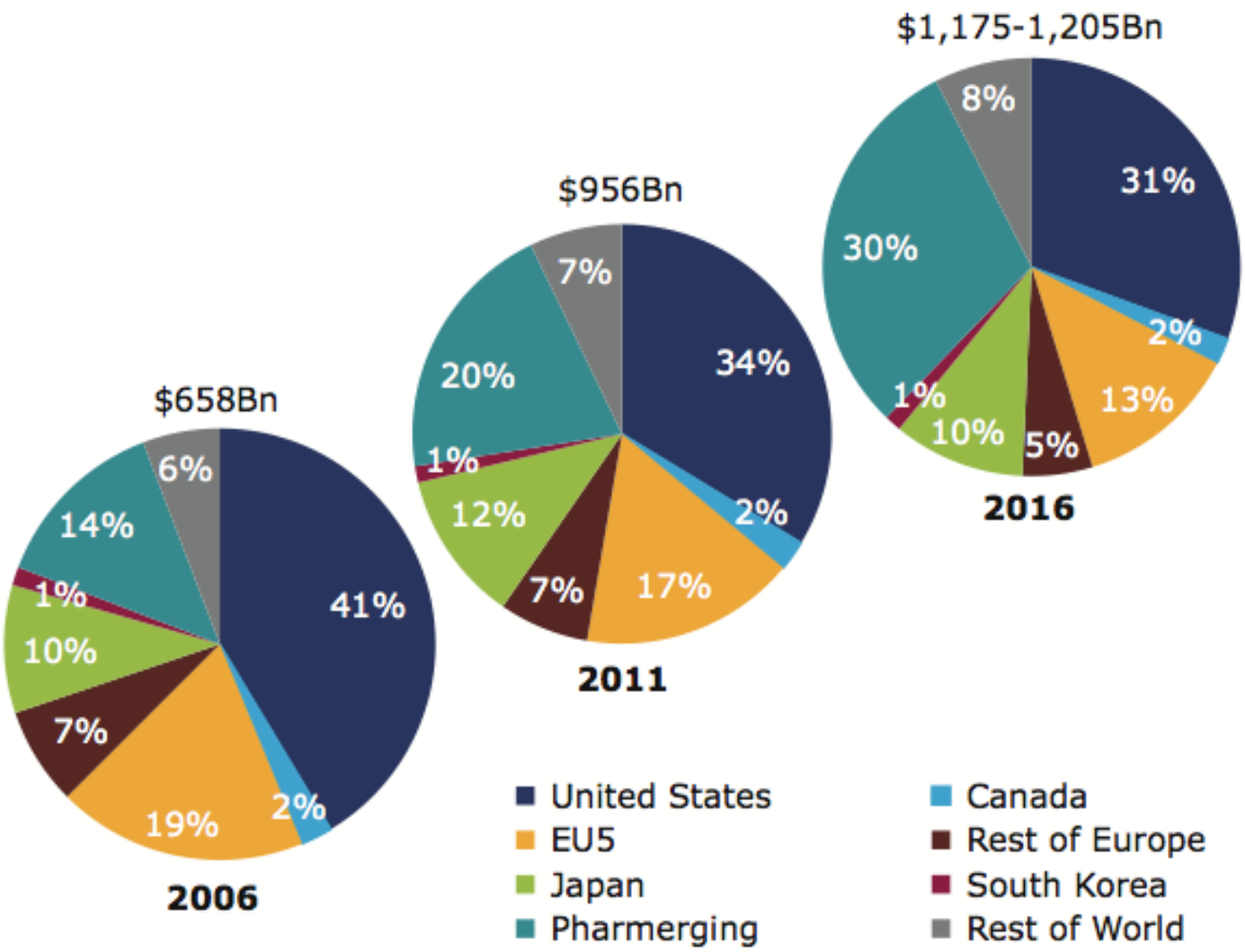
- Spending ~ $1.2 Trillion
- Spending on Brands $615-645Bn
- Spending on Generics $400-430Bn
- Developed Country Spending Per Person $609
- Pharmerging Country Spending Per Person $91

Key 2012–2016 Numbers

- New Molecular Entity Launches 160-185
- Global Spending Growth CAGR 3-6%
- U.S. Spending Growth CAGR 1-4%
- Pharmerging Spending Growth CAGR 12-15%
- "Patent Dividend" $106Bn

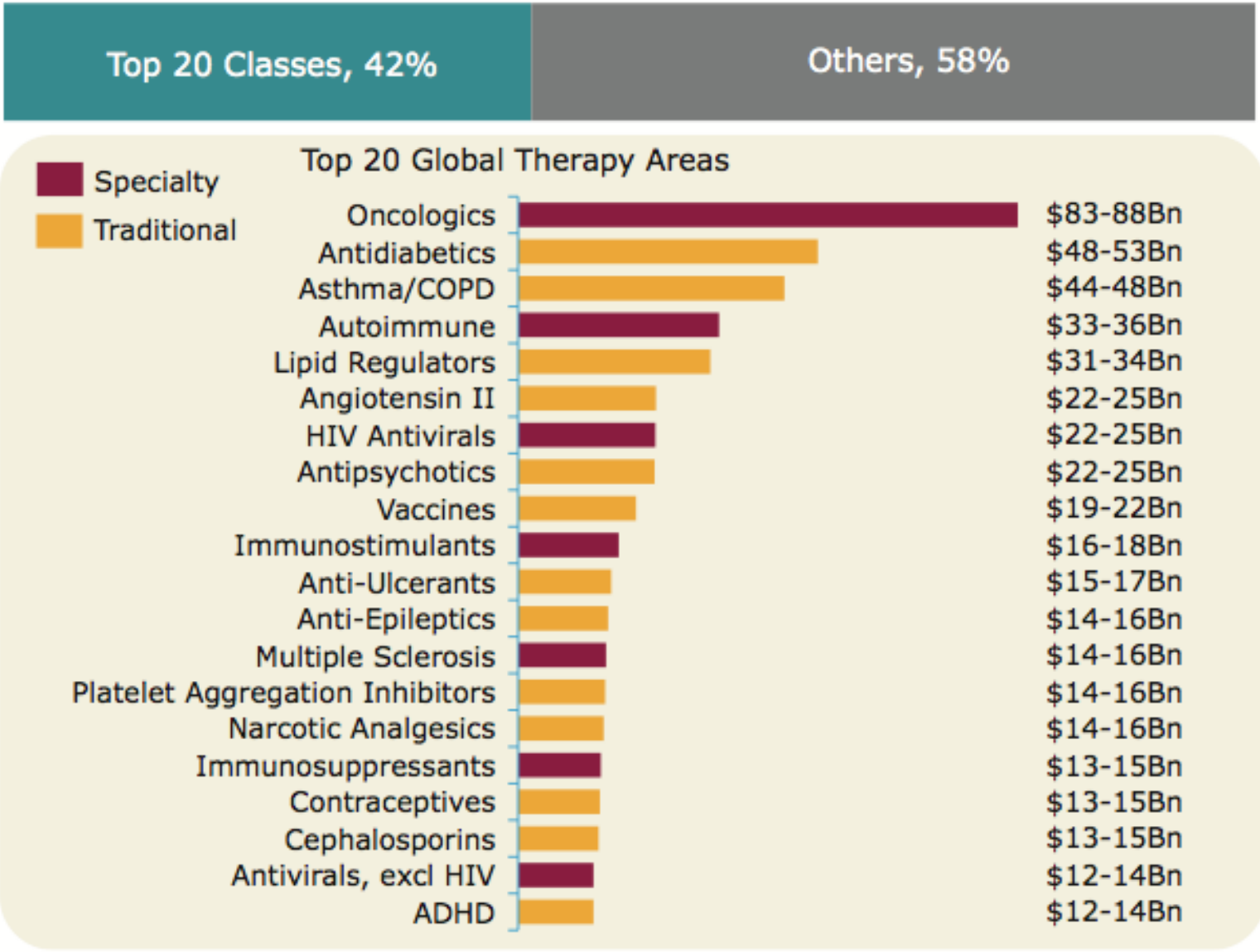
Global use of Medicines: Outlook throu' 2016, IMS health, July 2012

Spending by Geography



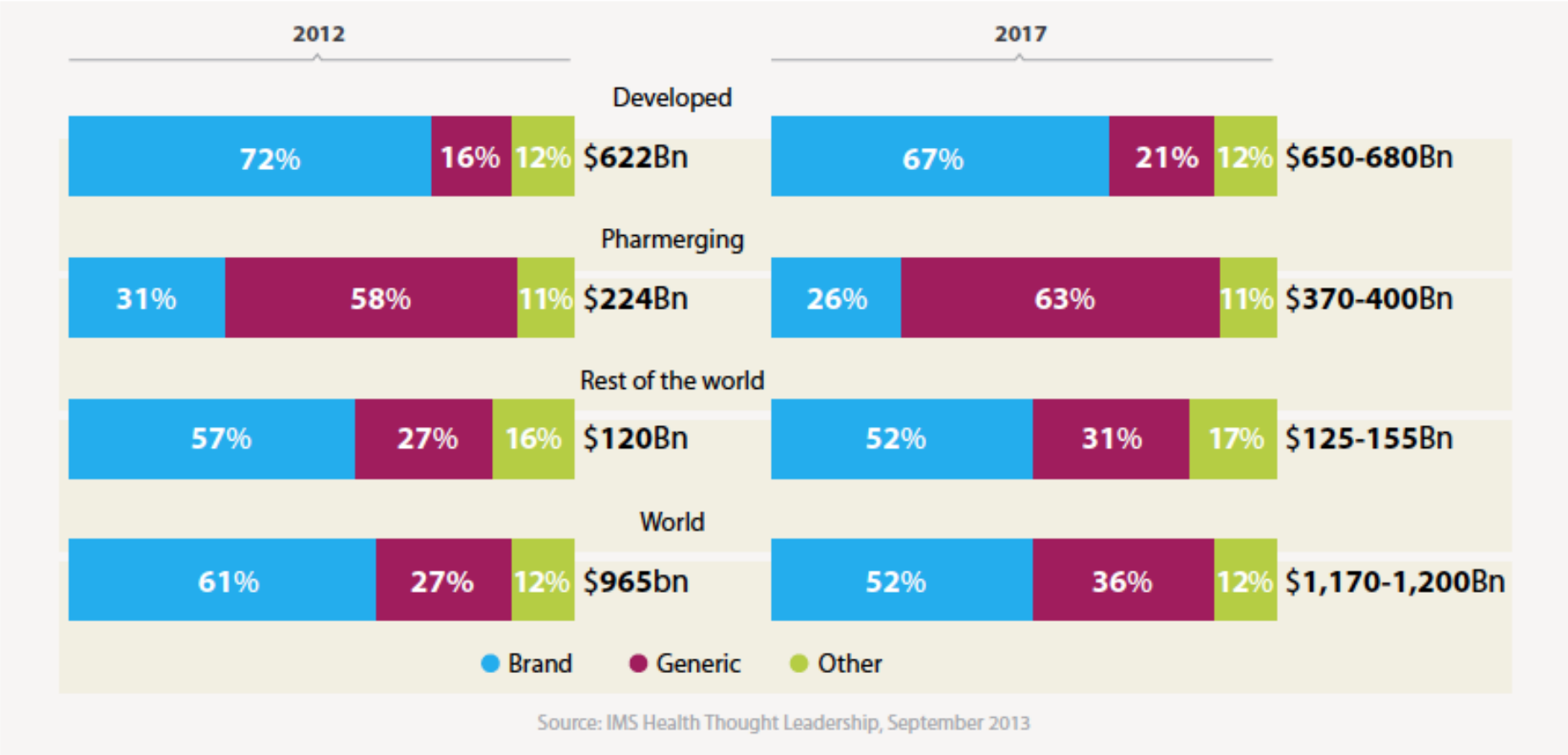
Global use of Medicines: Outlook throu' 2016, IMS health, July 2012

Spending in 2016



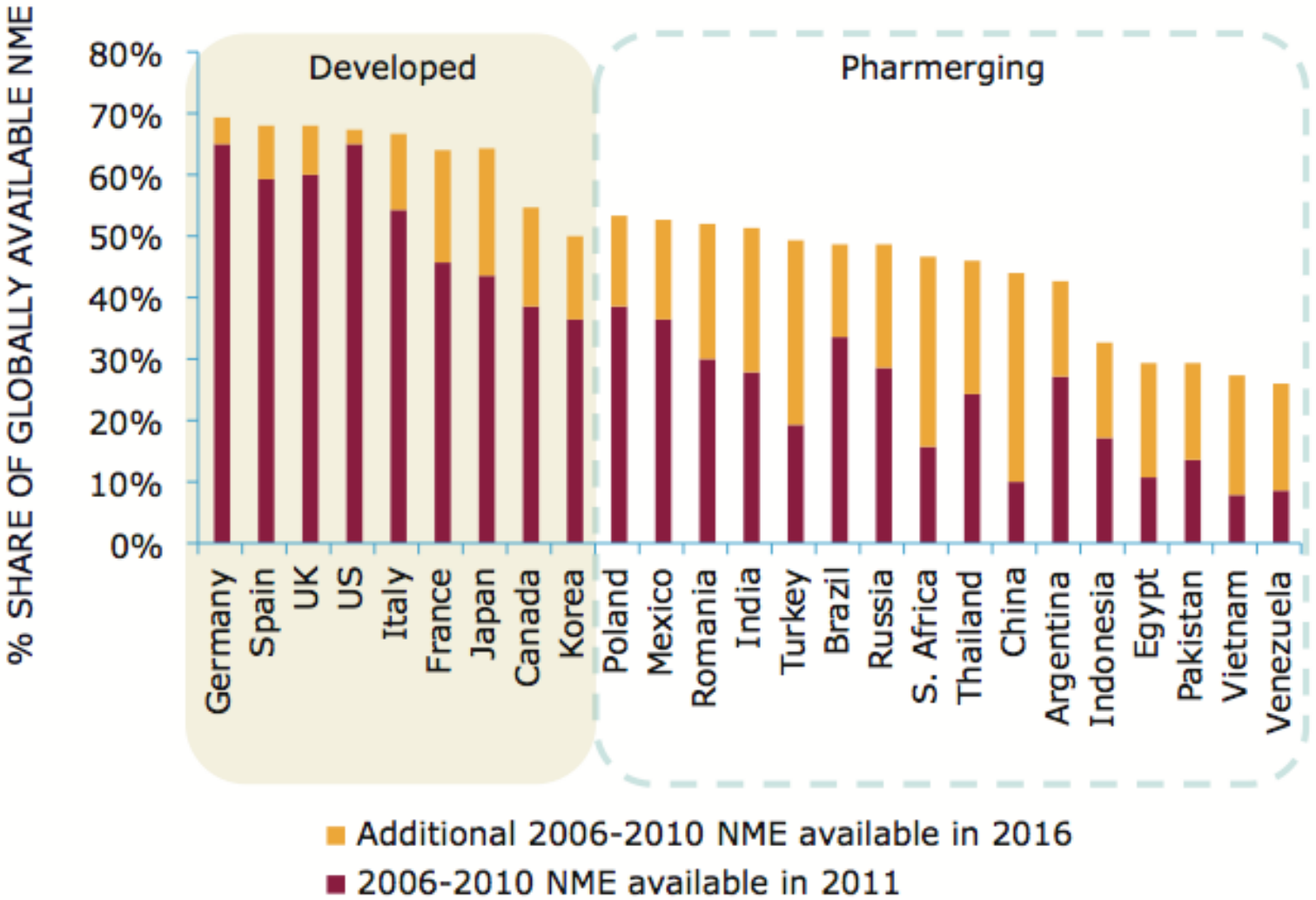
Global use of Medicines: Outlook throu' 2016, IMS health, July 2012

Global Spending, 2012 and 2017



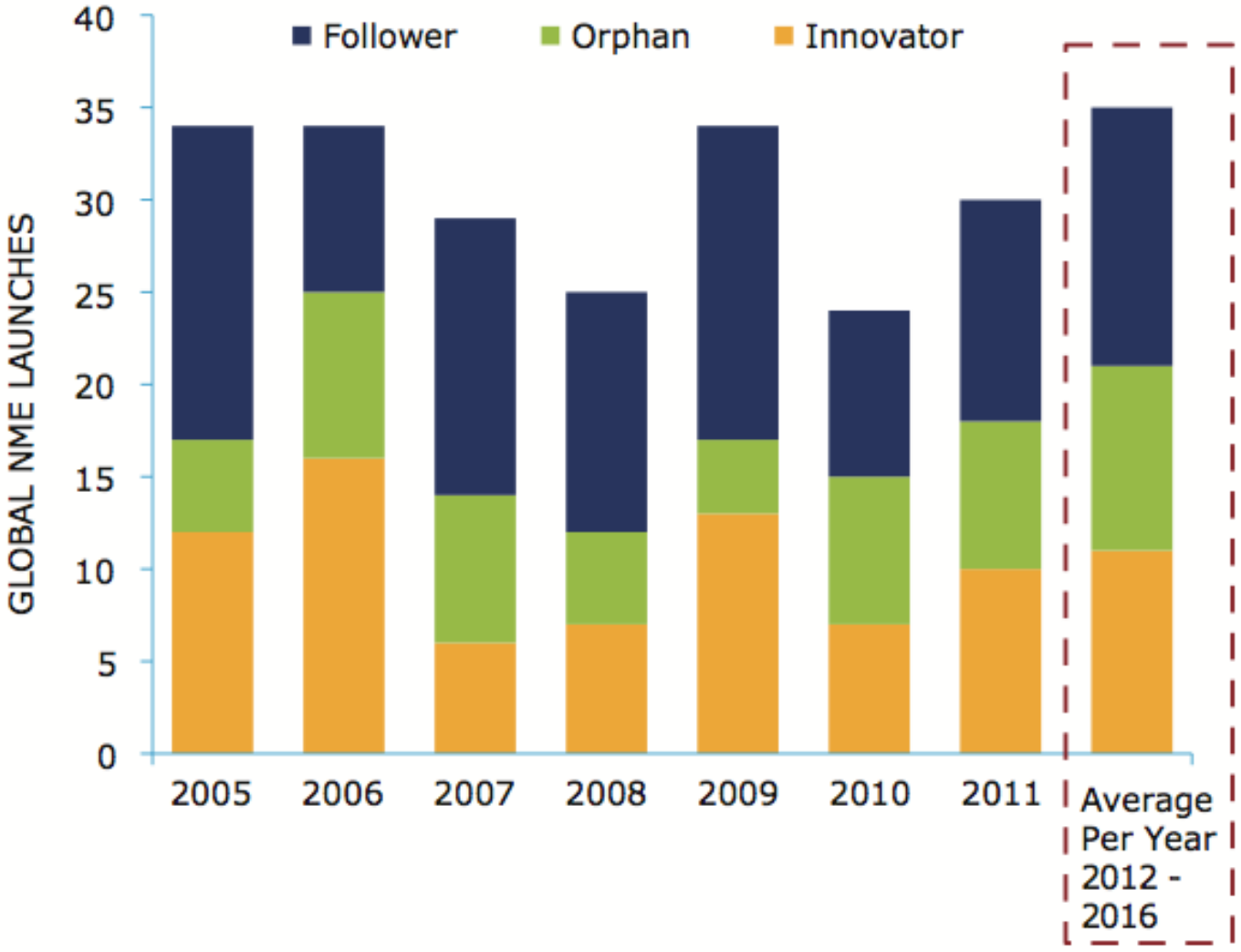
Generics will continue to dominate growth in spending in pharma-emerging markets and will account for 63% of the total market at the end of the forecast period.

Global New Molecular Entities Country Availability



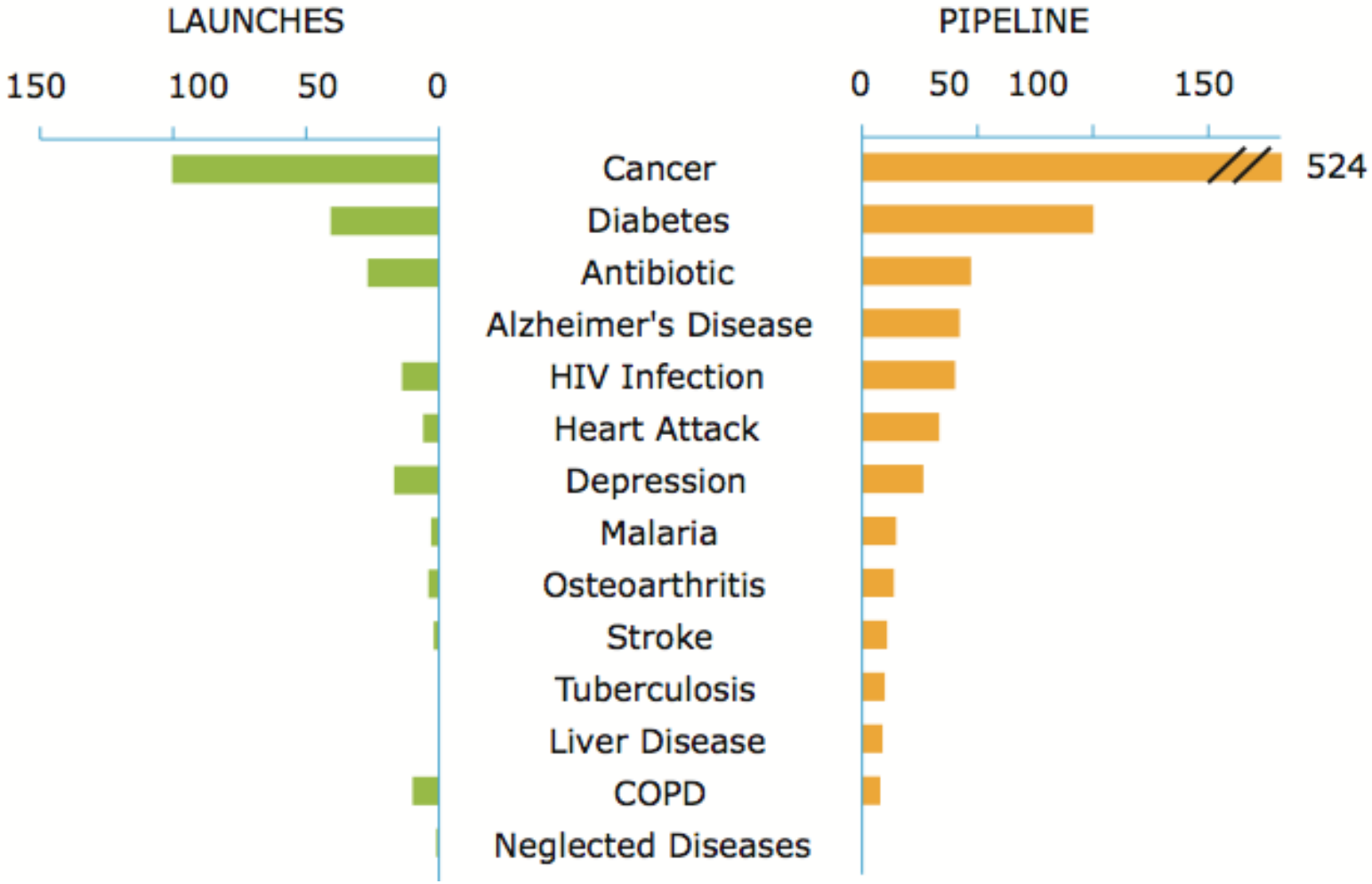
Global use of Medicines: Outlook throu' 2016, IMS health, July 2012

Global Launches of New Molecular Entities



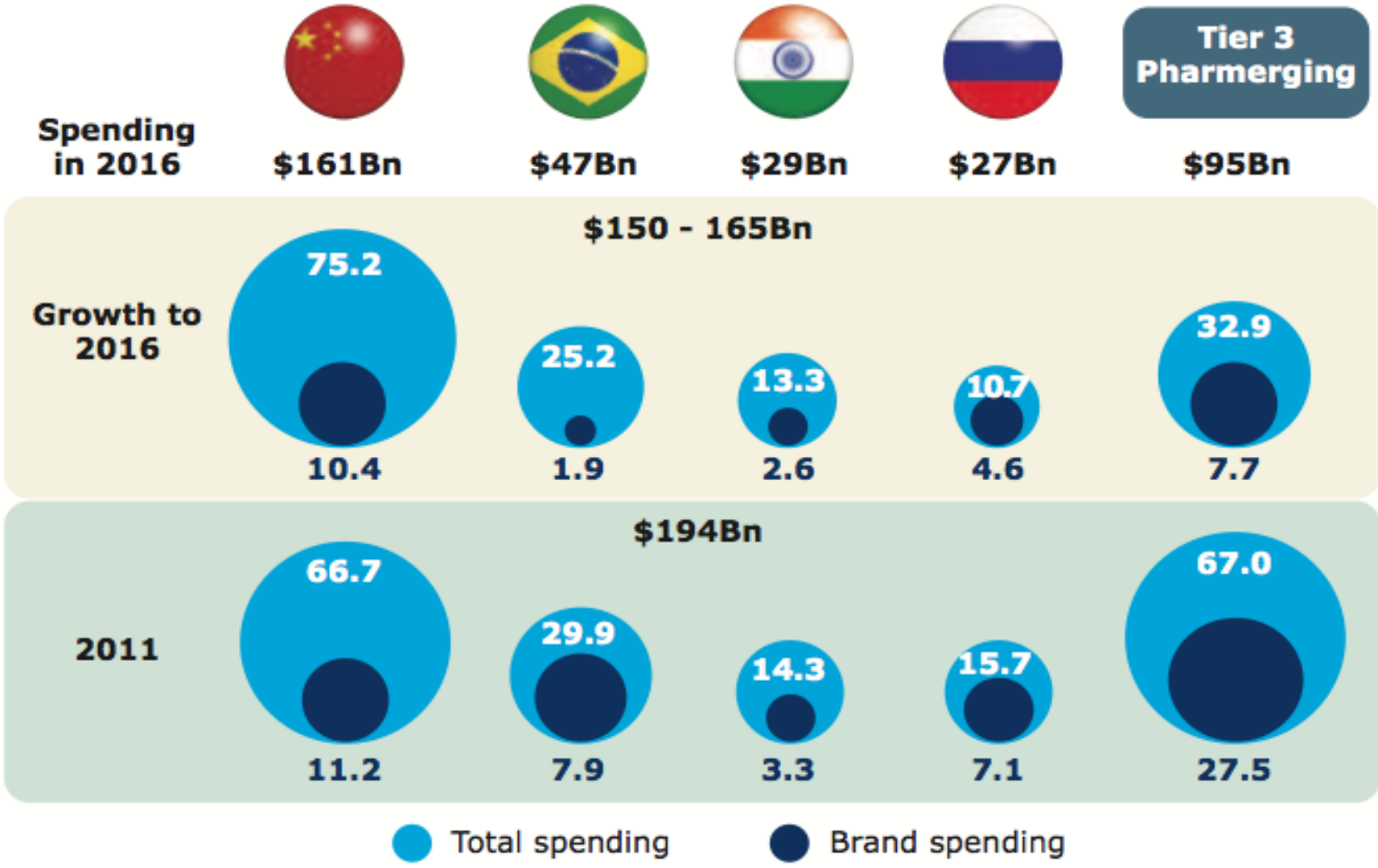
Global use of Medicines: Outlook throu' 2016, IMS health, July 2012

Launches & Pipeline in Priority Diseases

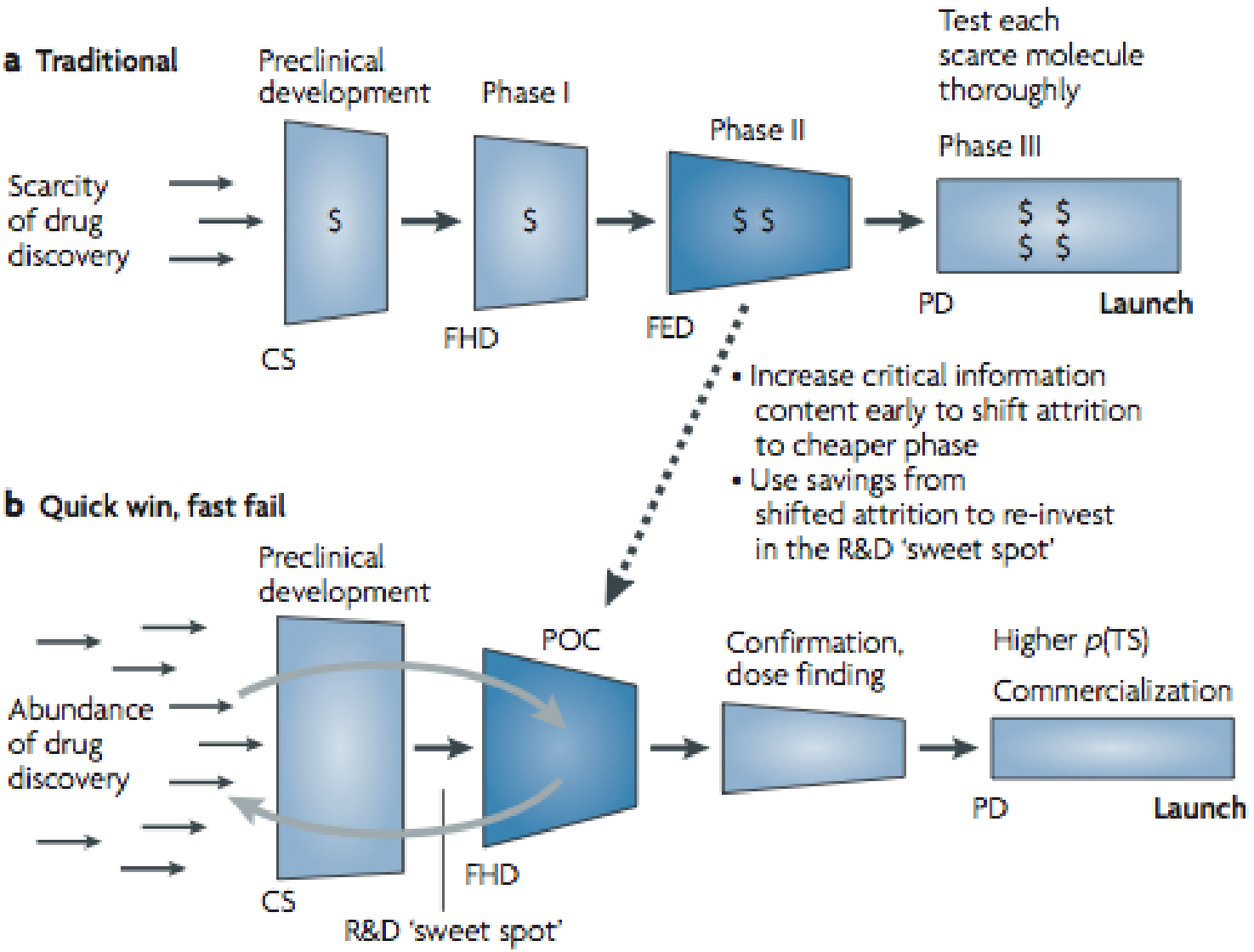


Global use of Medicines: Outlook throu' 2016, IMS health, July 2012

Pharmerging Spending and Growth



Global use of Medicines: Outlook throu' 2016, IMS health, July 2012



Nature Drug Discovery 2010 March; (9) : 211 - 213

Drug Information Journal
46(4) 455-463

DOI: 10.1177/0092861512446807
http://dij.sagepub.com

A Comparison of the Quality of Data, Assessed Using Query Rates, From Clinical Trials Conducted Across Developed Versus Emerging Global Regions

Pankaj B. Desai, PhD[1], Christopher Anderson[1,2], and William K. Sietsema[1,2]

Abstract

With increasing globalization of clinical trials, there is a growing concern regarding the quality of data generated from clinical studies conducted in some of the emerging regions. This concern has not been comprehensively addressed thus far because there is limited public access to restricted databases. In this study, we utilized data from 26 large phase II/III trials conducted in multiple regions of the globe by members of the Association of Clinical Research Organization and compared query rates, one of the few measurable parameters of quality of clinical trials data, between different global regions. A query is generated when a discrepancy is noted between protocol or source data and the case report forms (CRFs). A resolution of such an inconsistency is necessitated, which may result in a database change. The studies included in our analyses were conducted at 4721 global sites enrolling 63,871 participants. Overall, the data set included 1.39 million queries, 7.5 million CRF pages, and 95 million data parameters. The number of queries for various regions was added for each trial and normalized to the number of CRF pages or to the number of CRF data parameters. The calculated mean query rates and database change rates were compared using parametric and non-parametric statistical approaches. None of these approaches revealed statistically significant differences in the query rates or the rate of database change when each region was compared to North America or Western Europe. Thus, a comparative assessment of query rates suggests that the quality of clinical trials conducted in emerging countries is consistent with those conducted in developed regions. Despite several limitations of our analyses and the multifaceted complexities of global clinical trials, our findings should alleviate some concerns regarding clinical studies conducted in emerging nations.

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- Overview
- Regulatory Perspective
- Global trends in Drug Development/ Clinical trials
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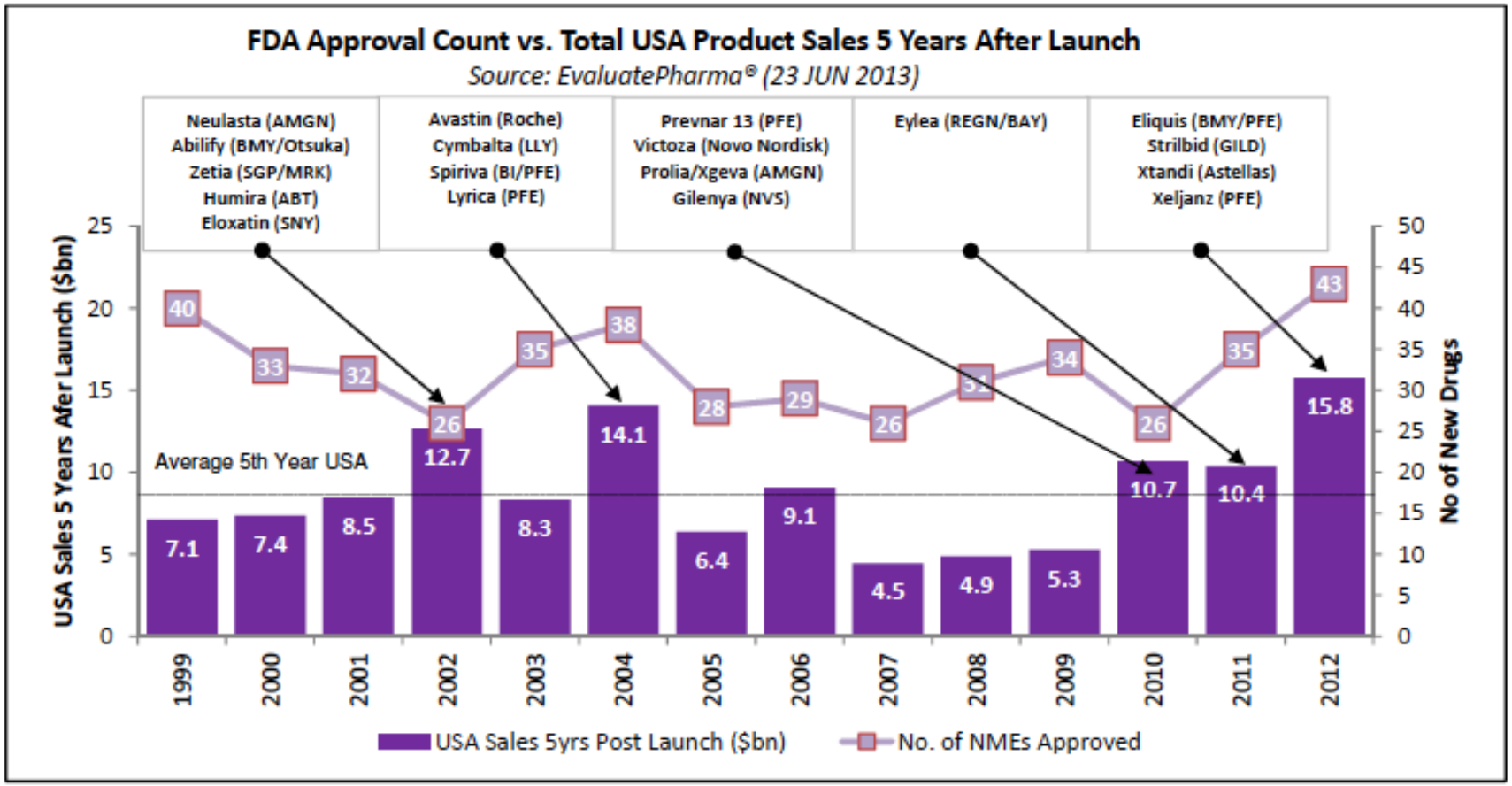


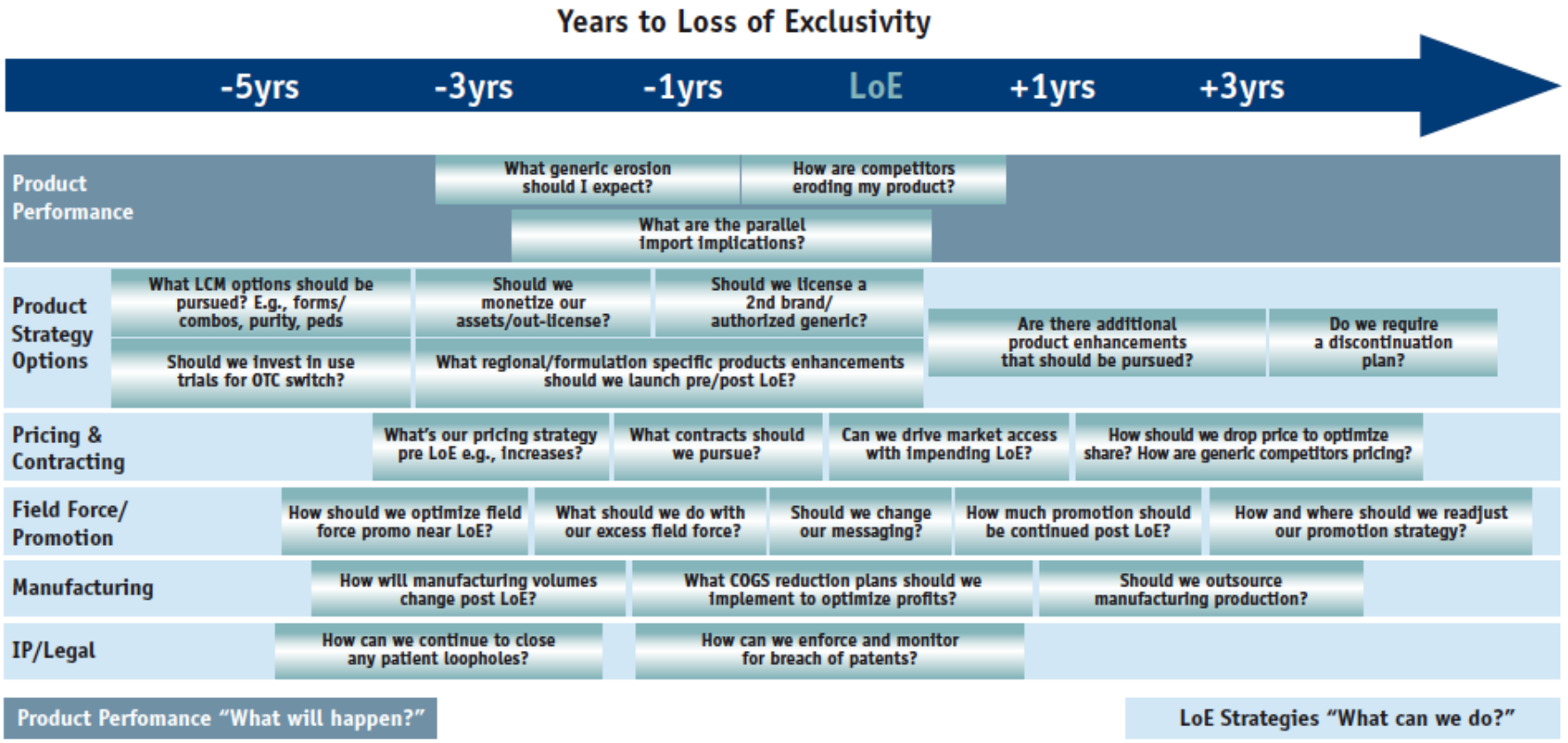
FDA Approval Count (NMEs & Biologicals) vs. 5th Year after Launch USA Product Sales

Year	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
No. of NMEs Approved	35	27	24	17	21	31	18	18	16	21	19	15	24	33
No. of Biologicals Approved	5	6	8	9	14	7	10	11	10	10	15	11	11	10
Total NMEs + Biologicals	**40**	**33**	**32**	**26**	**35**	**38**	**28**	**29**	**26**	**31**	**34**	**26**	**35**	**43**
% Chg.		*-18%*	*-3%*	*-19%*	*+35%*	*+9%*	*-26%*	*+4%*	*-10%*	*+19%*	*+10%*	*-24%*	*+35%*	*+23%*
USA Sales 5yrs Post Launch $bn	7.1	7.4	8.5	12.7	8.3	14.1	6.4	9.1	4.5	4.9	5.3	10.7	10.4	15.8
% Chg.		*+4%*	*+14%*	*+50%*	*-34%*	*+69%*	*-55%*	*+42%*	*-51%*	*+10%*	*+8%*	*+103%*	*-3%*	*+52%*
5yr USA Sales per Approval $m	178	224	264	487	238	371	228	313	172	158	155	411	297	367
% Chg.		*+26%*	*+18%*	*+84%*	*-51%*	*+56%*	*-39%*	*+38%*	*-45%*	*-8%*	*-2%*	*+165%*	*-28%*	*+23%*

Evaluate Pharma: World Preview 2013 Outlook to 2018

Figure 4

Critical decisions need to be made impacting many parts of the organization



LoE Planning & Life Cycle Management

Ref: Deloitte Report : The Future of LifeSciences Industry : Strategies for Success in 2015

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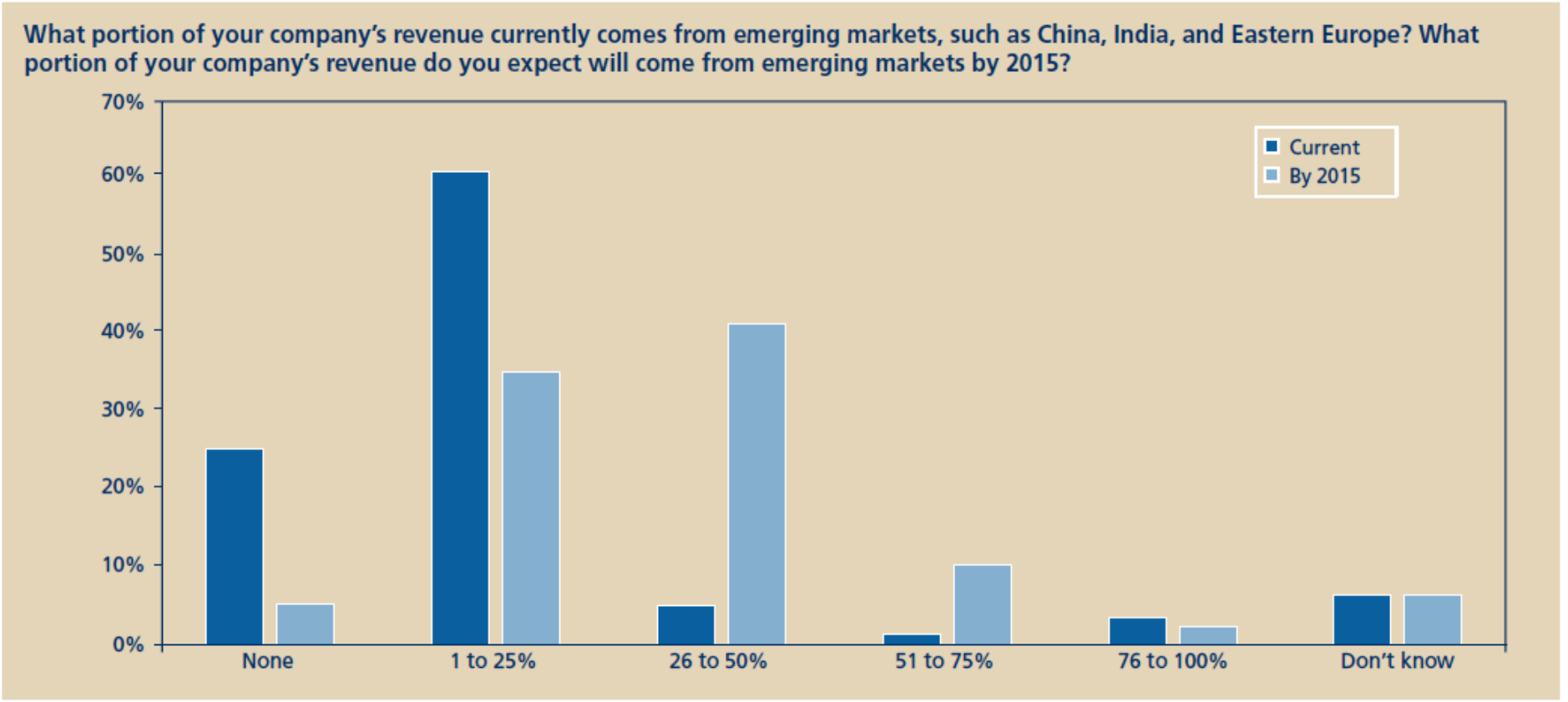
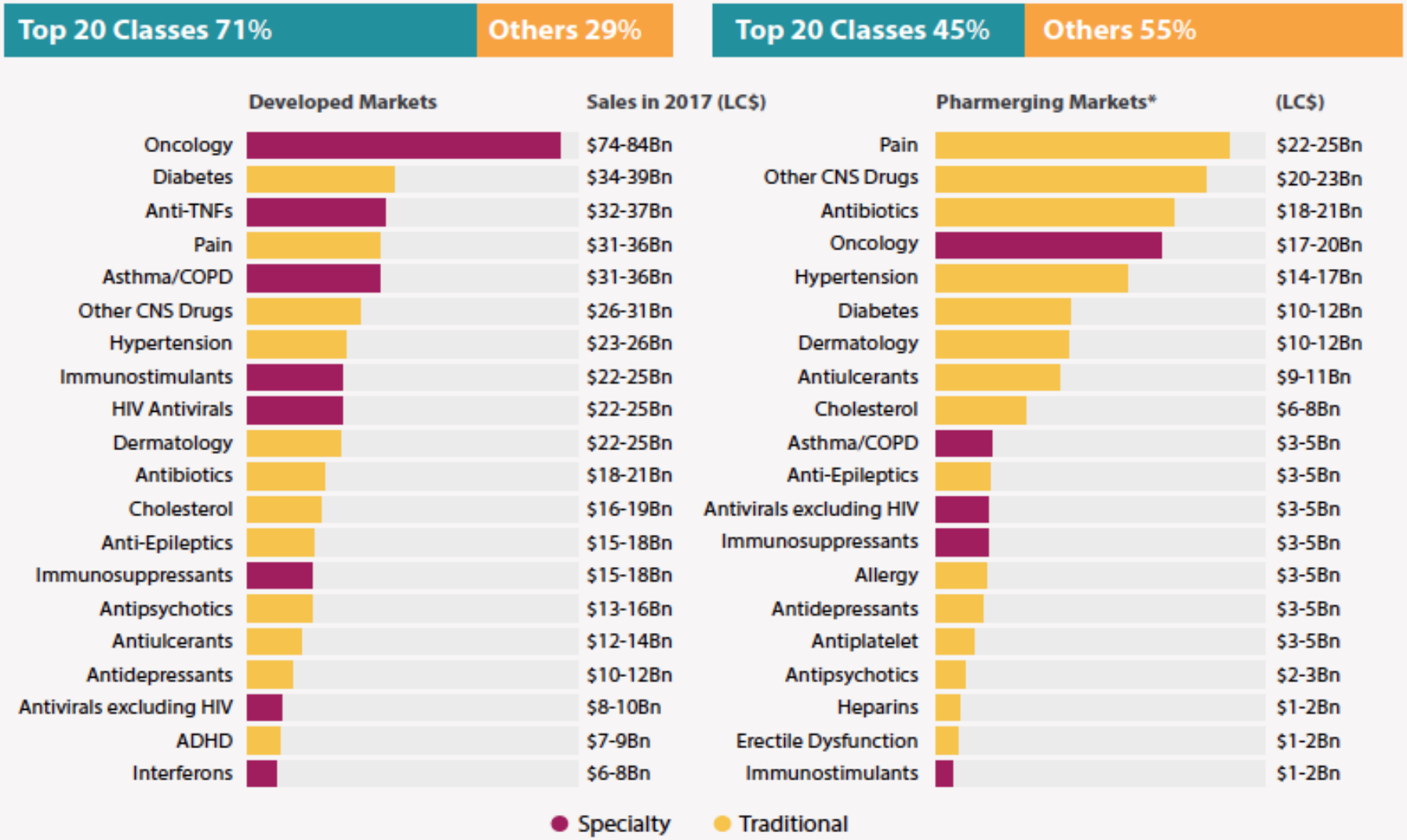


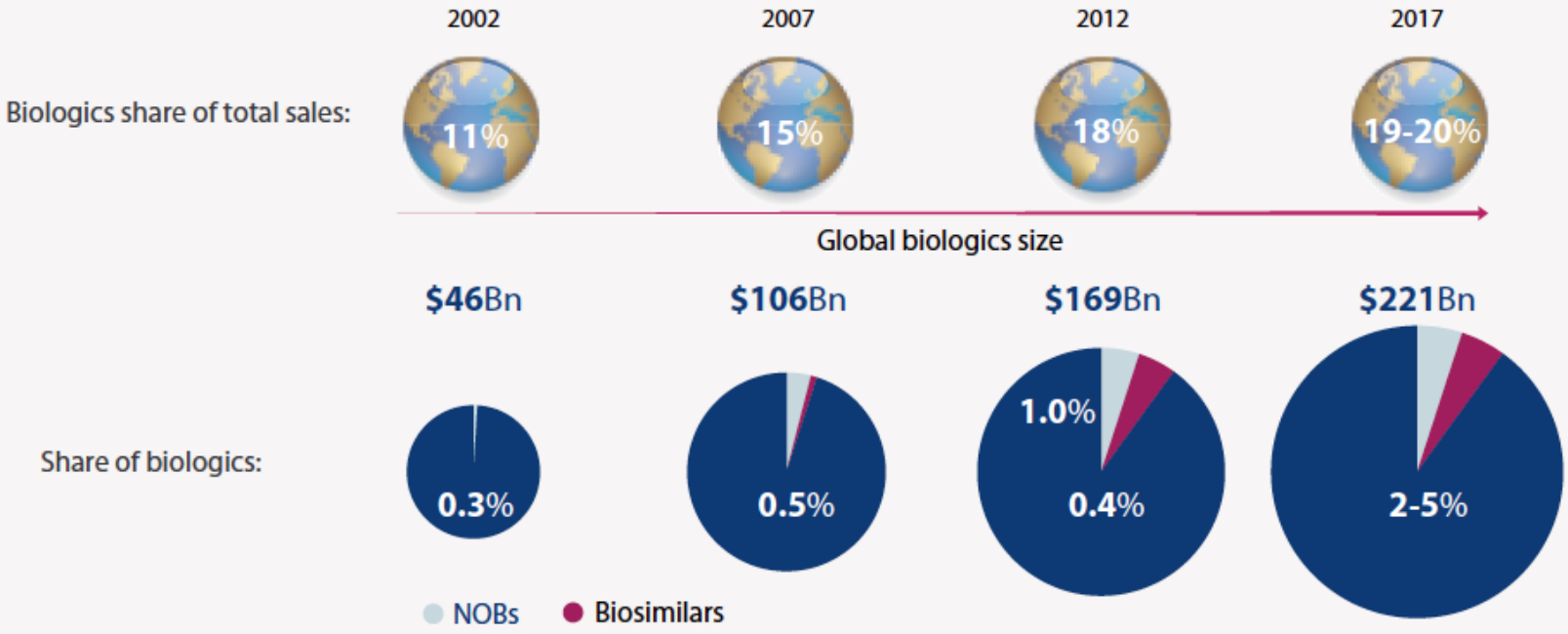
Ref: Deloitte Report : The Future of LifeSciences Industry : Strategies for Success in 2015

Spending by Therapy Area in 2017



Source: IMS Health Thought Leadership, September 2013

The biologics market



Source: IMS Health Thought Leadership, September 2013

Table 1 Key R&D, publication, patenting, and pharmaceutical market indicators for China, India, Brazil, South Africa and select developed markets

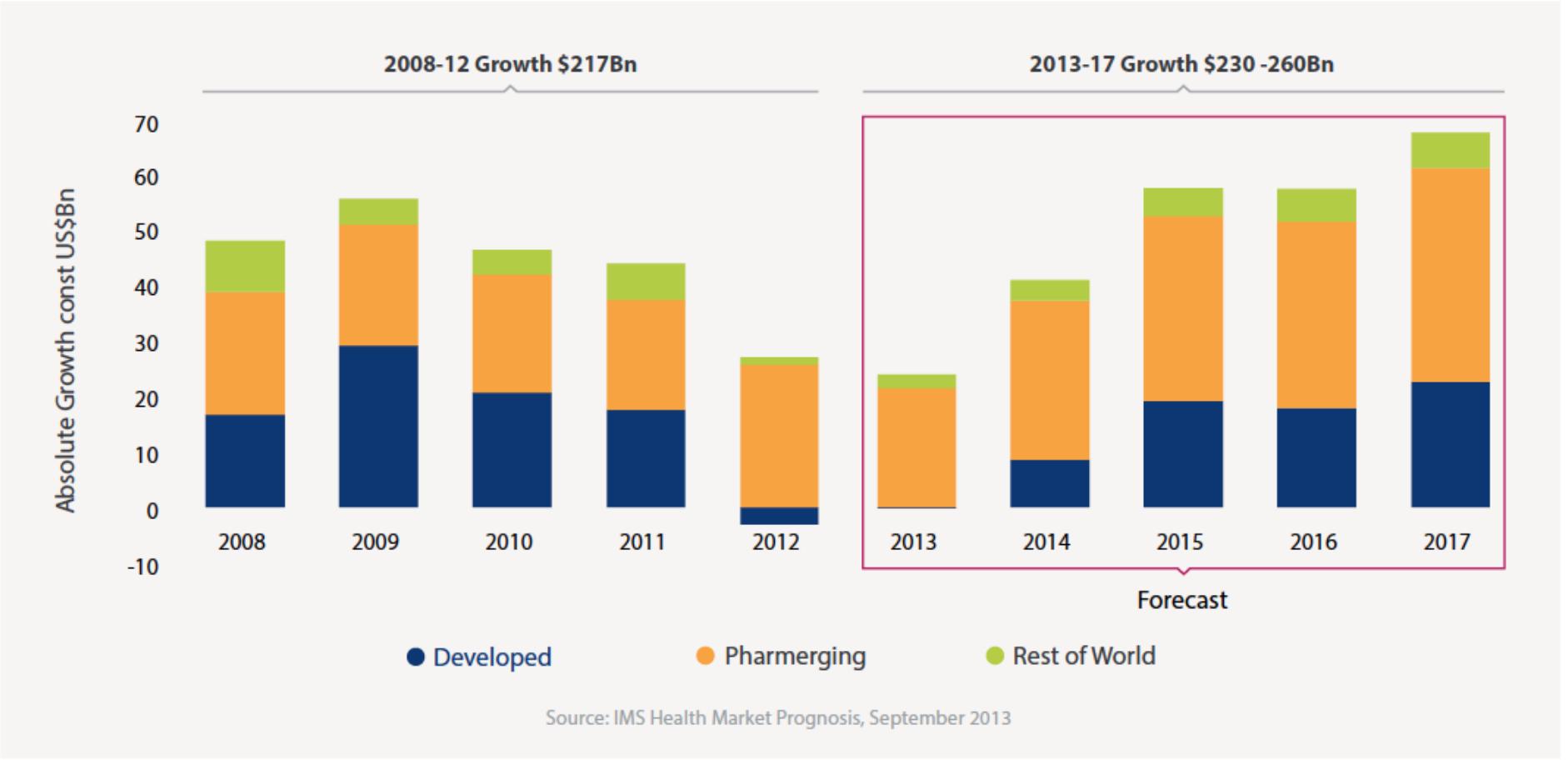
Country	R&D Expenditure as a % of GDP[1]	Gross Expenditure on R&D in Billions USD[1]	Share of Global Scientific Publications [Annual Growth Rate b/w 2000–2008][2]	Annual Growth Rate in Patenting (2000–2006)[2]	Pharmaceutical Market Size, Billions USD, 2010 (Projected Size in 2015)[3]	CAGR for Pharmaceutical Market, 2006–2010 (2010–2015 Forecast)[3]
China	1.5 (2008)	102	12%, [23.4%]	26.5%	25.7 (48.8)	17.3% (13.6%)
India	0.80	24.8	2.3%, [4.7%]**	42%*	14.1 (30.4)	16.6% (16.6%)
Brazil	1.10	20.3	1.6%, [12.2%]***	N/A	15.3 (34.4)	13.1% (17.6%)
Canada	1.84 (2008)	24.0	2.7%	3.9%	26.6 (30.2)	5.4% (2.6%)
Germany	2.54	72.2	4%08	5.7%	37.9 (41.5)	3.4% (1.8%)
Japan	3.44	148	4.8%	4.5%	72.4 (102.7)	4.4% (7.2%) ****
United States	2.82 (2008)	398	16%	2.6%	292.8 (344.7)	2.9% (3.3%)

Sources: [1] UNESCO Science Report 2010. Data is for 2007 unless stated otherwise.
[2] OECD Science, Technology and Industry Outlook 2010. Share of publications is for 2008, except for India where this share represents 2006 Data.
[3] DataMonitor 2010, Country-specific Pharmaceutical Industry Profile Reports.
* Estimate for India is for period 1997–2004.
** Estimate for India is for 1995–2005.
*** Estimate for Brazil is for 1998–2008.
**** Data for 2005–2009 and 2009–1014.
CAGR stands for Cumulative Annual Growth Rate.

Growth in the emerging countries continues to outpace the developed countries.

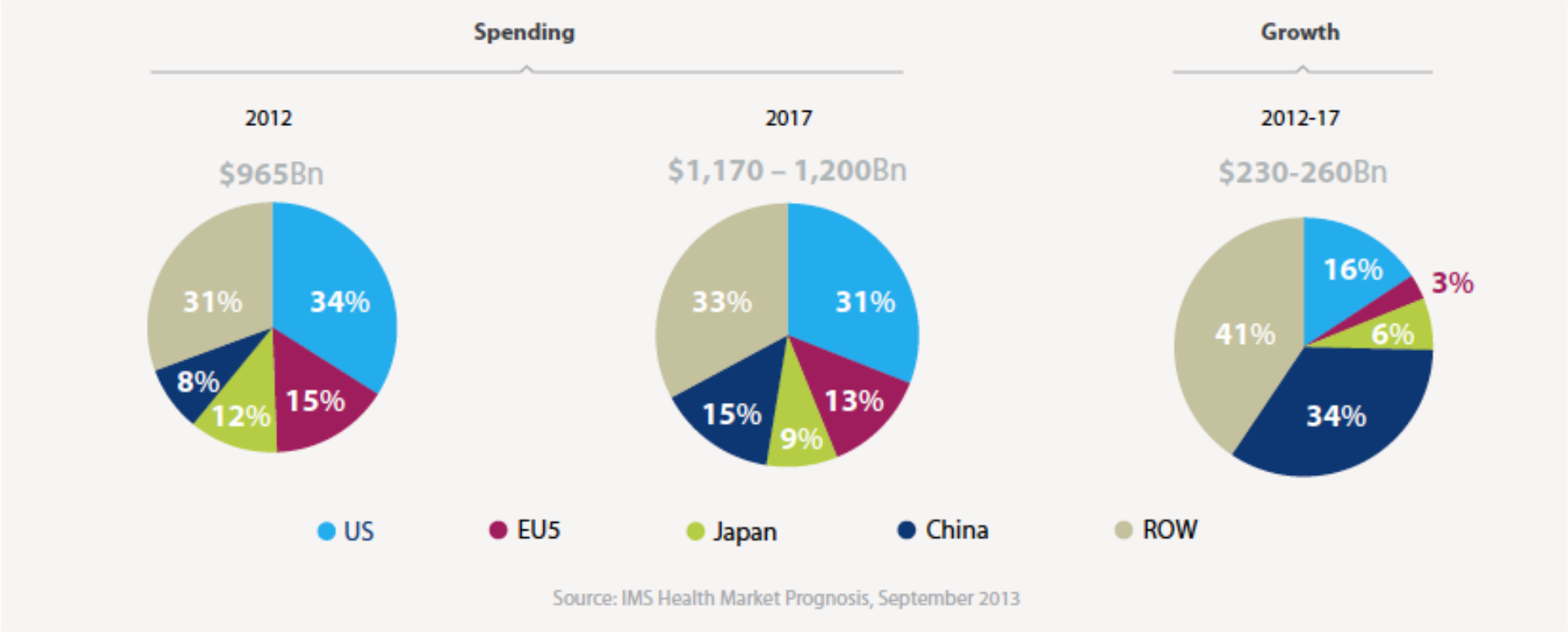
Rezaie et al. Health Research Policy and Systems 2012, 10:18

Global Growth, 2008-2017



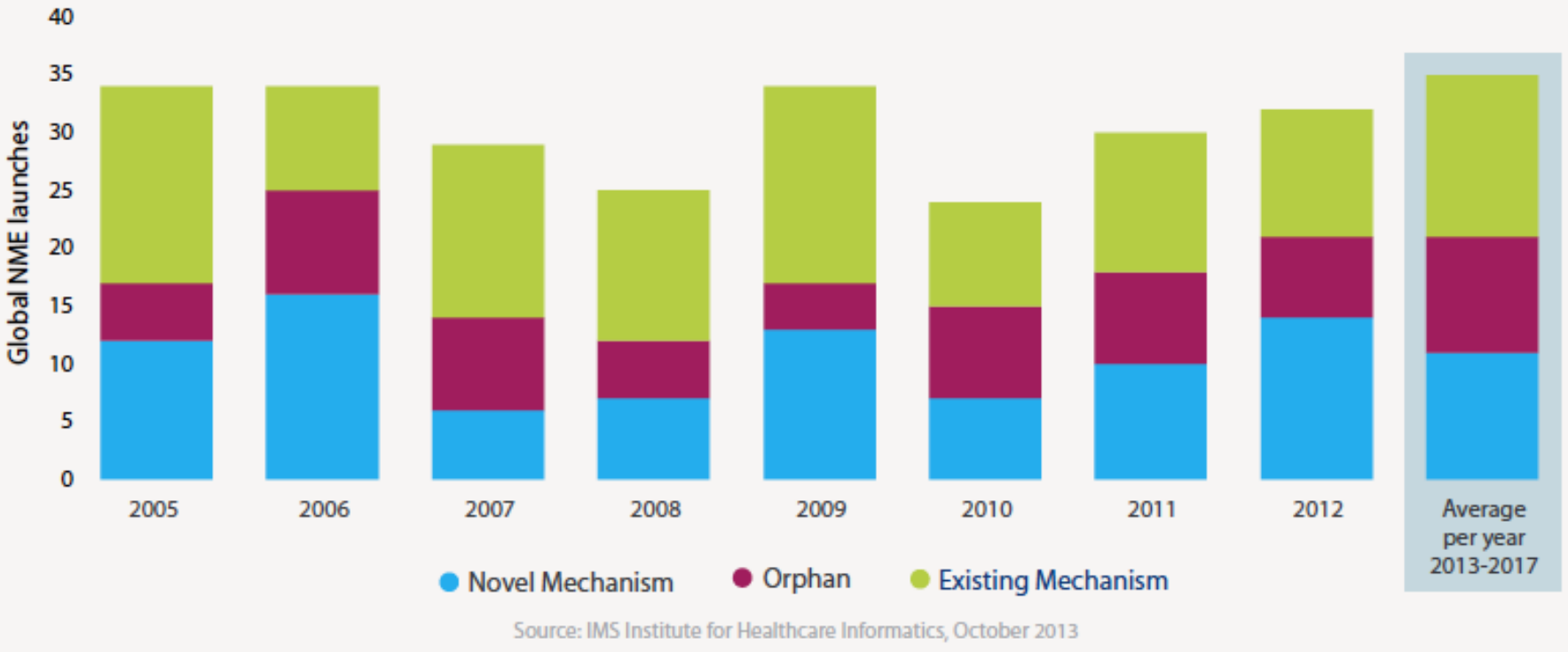
Growth in pharma - emerging markets will increase from $26Bn in 2012, to $30-50Bn in 2017, primarily due to increased access to medicines as infrastructure and health systems evolve.

Geographic distribution of medicine spending



The U.S., EU5, Japan and China account for just under 70% of total global medicine spending

Global Launches of New Molecular Entities



Increasing numbers of innovative new medicines and orphan drugs are expected to be launched.

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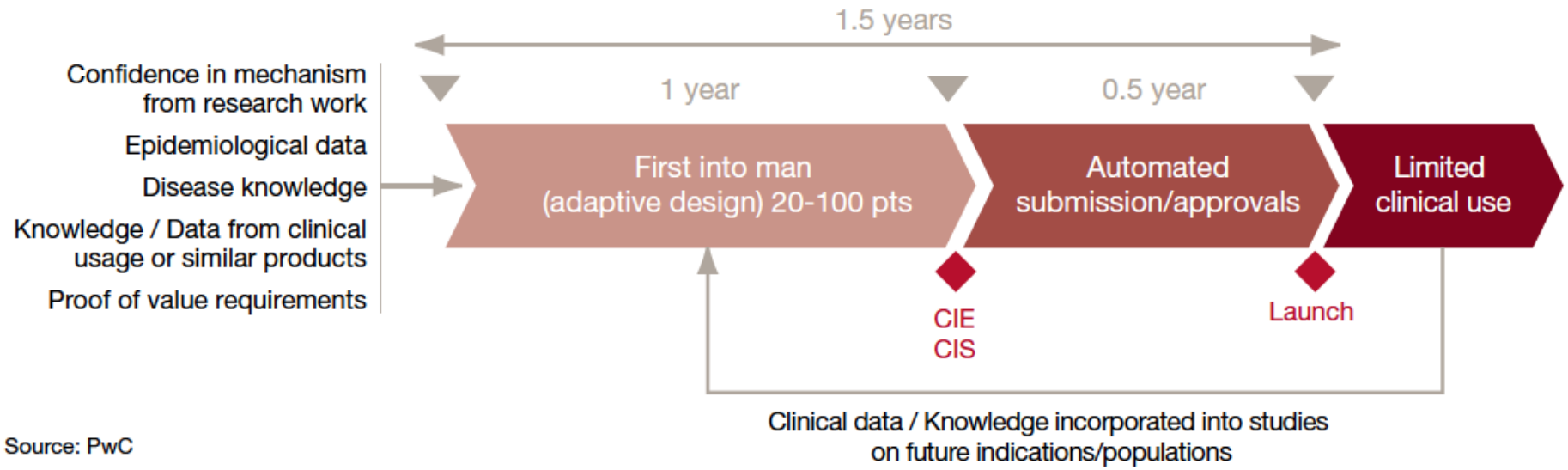
Global Challenges

- Regulatory approval
- Medical Infrastructure
  - Addressing adverse events
  - Access to healthcare system
  - Access to specialists
  - Training Investigators
- Culture & Language
- Geography

Global Challenges



Source: PwC

Development process in 2020

Strategic area 1: addressing public-health needs

Objectives[22]	Impact/result indicators
Stimulate medicines development in areas of unmet medical needs, neglected diseases and rare diseases, and for all types of medicines for veterinary use.	• Increase in the number of scientific-advice requests for medicines for unmet medical needs, neglected diseases and rare diseases, and for all types of medicines for veterinary use. • Increase in the use of specific procedures such as Article 58 procedures (under Regulation (EC) No 726/2004).
Facilitate new approaches to medicines development.	• Existing model for medicines regulation is adapted to enable integration of new and emerging science.
Apply a more proactive approach to public-health threats where medicines are implicated.	• Effective preparedness mechanisms that take due account of learnings from previous public-health threats/crisis situations are available. • The 'One World, One Health' concept is applied to link the protection and improvement of animal health with the protection and improvement of human health. • The Committee for Medicinal Products for Veterinary Use (CVMP) Strategy on Antimicrobials 2011-2015[23] is successfully completed.

EMA Roadmap 2015

Strategic area 2: facilitating access to medicines

Objectives	Impact/result indicators
Address the high attrition rate during the medicines-development process.	• Increase in the percentage of successful marketing-authorisation applications for new medicinal products by encouraging that scientific advice is sought and adhered to. • Scientific information on failed medicines-development processes is made available to the scientific community.
Reinforce the benefit/risk-balance assessment model.	• Increased inclusion of quantitative elements, alongside an improved elaboration of the rationale for the decision/opinion in the benefit/risk considerations, for subsequent publication in the European public assessment reports (EPARs) (medicines for human use). • The concept and practice of benefit/risk assessment are embedded as part of the scientific-review process and subsequently communicated in EPARs as part of the methodology used for assessment (medicines for veterinary use).
Continue to improve the quality and the regulatory and scientific consistency of the outcome of the scientific review.	• Structured external surveys performed by the Agency's stakeholders on the outcome of the scientific reviews demonstrate an increase in the quality and the consistency.

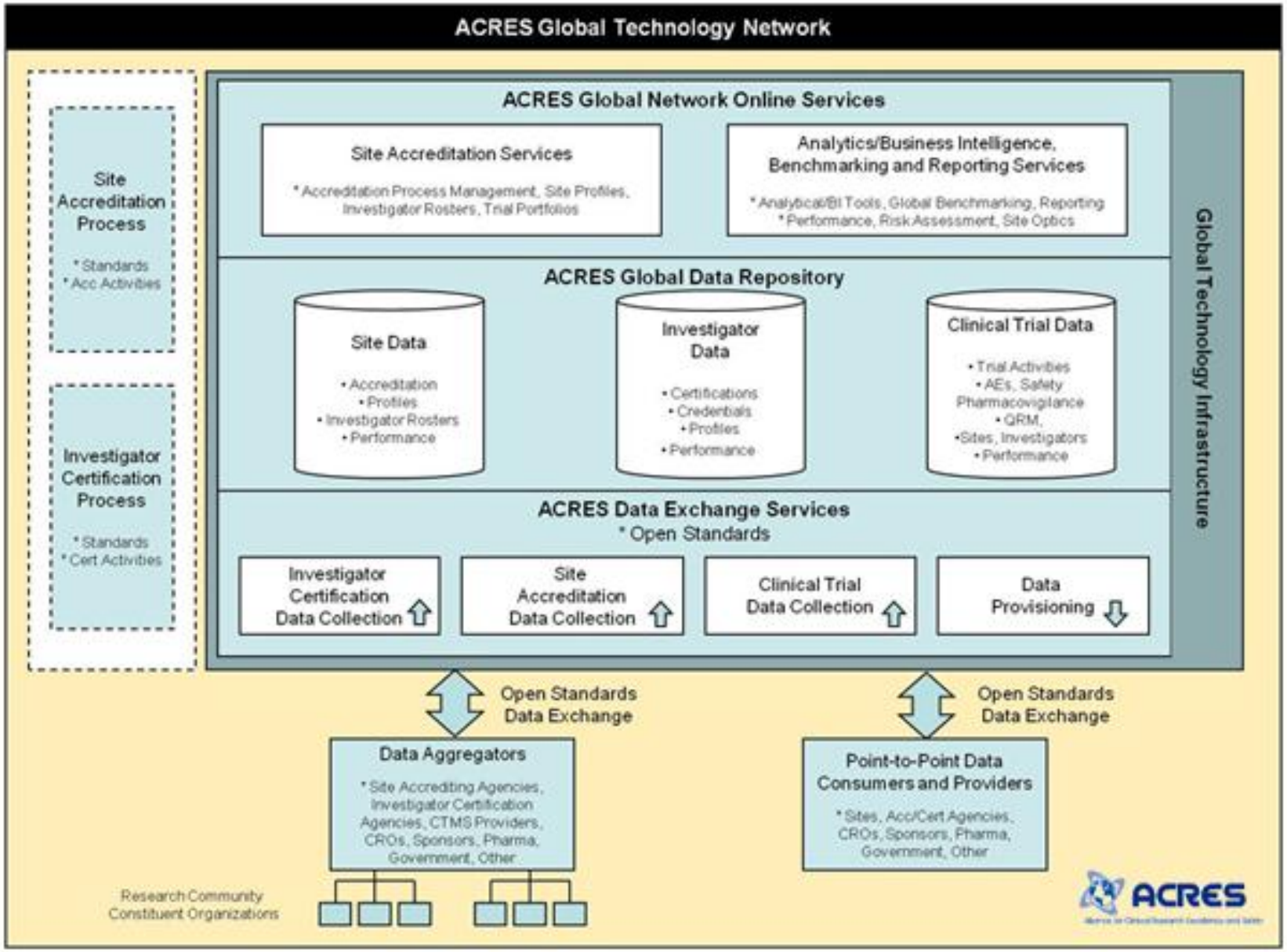
EMA Roadmap 2015

Strategic area 3: optimising the safe and rational use of medicines

Objectives	Impact/result indicators
Strengthen the evidence base in the post-authorisation phase to enable better regulatory decision-making.	• A regulatory model that facilitates the post-authorisation collection of data on benefits and risks of medicinal products is put at the disposal of the regulatory system. • A pharmacovigilance framework appropriate to the needs and priorities of the veterinary sector is developed as an outcome of the European Commission's impact assessment of the legislation for veterinary medicines.
Enhance patient safety by avoiding unnecessary risks to patients as a result of the use of medicines.	• A revised risk-management concept that targets both novel pharmacovigilance methodologies and a risk-minimisation toolbox better adapted to reduce harm is available.
Become a reference point for information on medicines evaluated by the Agency.	• A high-quality, informative and targeted set of information on medicines falling within the sphere of the Agency's responsibilities is proactively put at the disposal of the EU regulatory network at the moment of licensing/updating of the marketing authorisation.
Improve the decision-making process by taking due account of patient experience, thus contributing to the rational use of medicines.	• Conclusions from outcomes-research projects analysing the impact of regulatory decisions on public health are used to provide input into future regulatory policy decision-making.

EMA Roadmap 2015

GLOBAL TECHNOLOGY NETWORK



TransCelerate BIOPHARMA INC.

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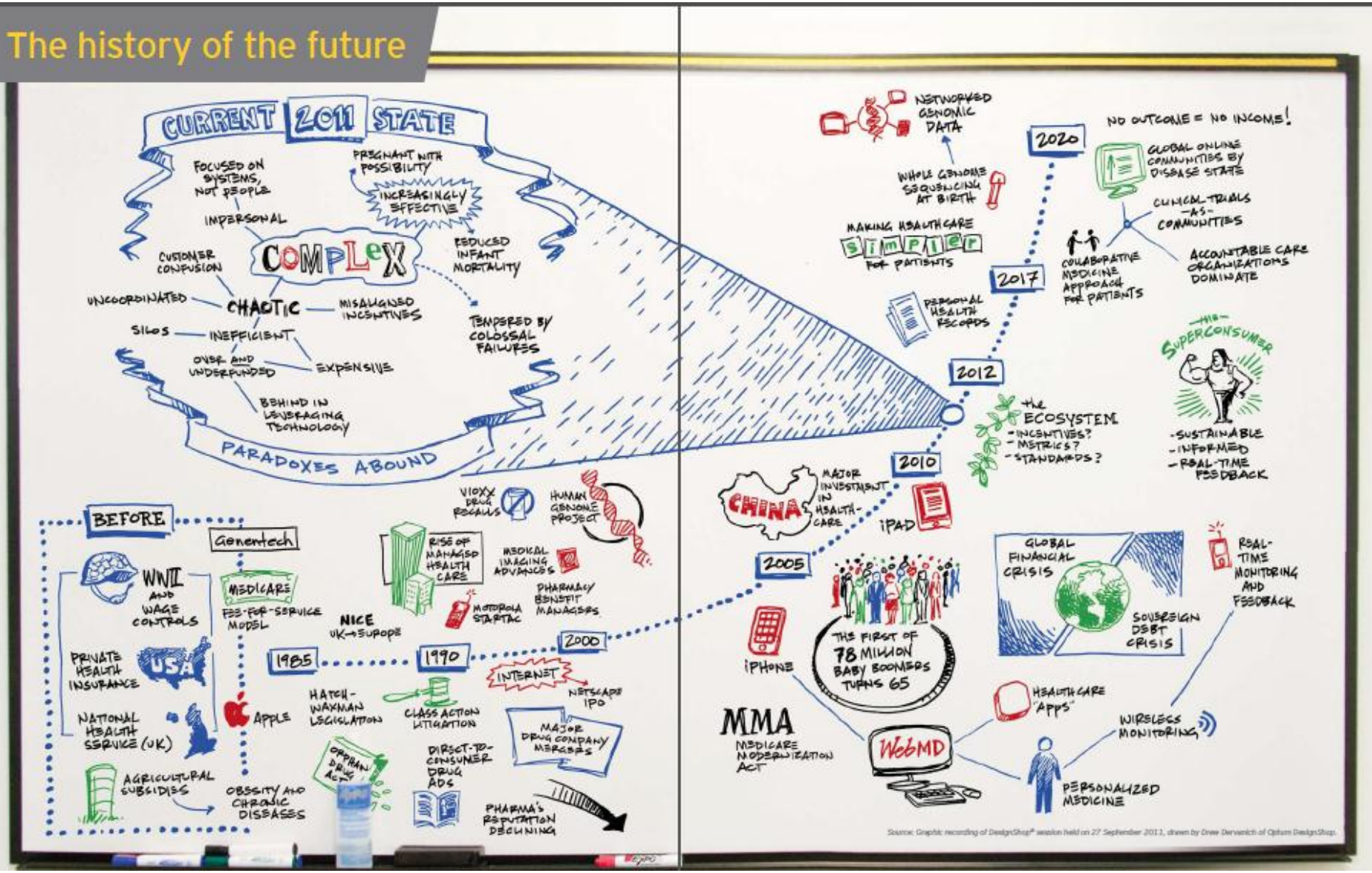
Our Initiatives

At launch, TransCelerate chose the following projects as initial areas of focus: development of risk-based site monitoring approach and standards, development of a shared user interface for investigator site portals, mutual recognition of study site qualification and training, development of clinical data standards, and establishment of a comparator drug supply model.

Risk-Based Monitoring | Site Qualification and Training | Clinical Data Standards | Comparator Drugs | Shared Investigator Portal

The history of the future



Progressions : Global Life Sciences, E & Y, 2012

Moving Ahead.

- Innovation, the ultimate engine of growth for the global provision of medicines, will see a revival of activity through 2017, with increases in the number of global innovative launches since 2010.
- Growth in pharma-emerging markets will increase from $26Bn in 2012, to $30-50Bn in 2017, primarily due to increased access to medicines as infrastructure and health systems evolve.
- Patient-centric approach will transform clinical development, as deep insights allow for more efficient product development and a better understanding of patients' needs.

Thank you