The review analyzes reasons for continued low productivity in pharmaceutical industry and discusses innovative model and strategies to boost productivity and build risk mitigated discovery portfolio.

Drug discovery in pharmaceutical industry: productivity challenges and trends

Ish Khanna

Kareus Therapeutics, 40 Rue Fritz Courvoisier, 2300 La Chaux-de-Fonds, Switzerland

Low productivity, rising R&D costs, dissipating proprietary products and dwindling pipelines are driving the pharmaceutical industry to unprecedented challenges and scrutiny. In this article I reflect on the current status of the pharmaceutical industry and reasons for continued low productivity. An emerging 'symbiotic model of innovation', that addresses underlying issues in drug failure and attempts to narrow gaps in current drug discovery processes, is discussed to boost productivity. The model emphasizes partnerships in innovation to deliver quality products in a cost-effective system. I also discuss diverse options to build a balanced research portfolio with higher potential for persistent delivery of drug molecules.

Ish Khanna
has over 28 years of pharmaceutical industry experience with success in advancing drug molecules from concept to clinic and market. He has held Technical Leadership and Senior Management positions in global pharmaceutical companies (*Pfizer, Pharmacia, Searle, Dr. Reddy's Labs, Kareus Therapeutics*) and has experience in building risk balanced discovery portfolio. Dr. Khanna's areas of expertise cover medicinal chemistry, understanding pharmacokinetic and pharmacodynamic properties of drug molecules and lead optimization strategies. He has keen interest and knowledge of emerging trends in pharmaceutical industry. He is co-inventor and co-author of over 100 patents and publications.

Pharma industry: an introduction

Innovation has always been the backbone and underlying strength of the pharmaceutical industry. During decades the industry has delivered multiple life-saving medicines contributing to new treatment options for several medical needs. Many diseases, particularly acute disorders, are now treatable or can be managed effectively. The discovery of new medications for cardiovascular, metabolic, arthritis, pain, depression, anxiety, oncology, gastrointestinal disorders, women health, infectious diseases and many others have led to improvement in health, quality of life and increased life expectancy. The decade of 1990s is considered a golden era in the pharmaceutical industry that yielded several blockbuster drugs and lifted the pharmaceutical sector and its select players to top ranks [1]. The years 1996 and 1997 were particularly impressive with record setting approval of 56 and 45 new molecular entities (NMEs) and biopharmaceutical entities (NBEs) by US FDA [2,3].

The large pharma companies generate the maximal revenues and spend the most in R&D activities. During 2010, the global revenues for pharmaceutical products were 856 billion dollars with US and Europe accounting to approximately 60% of these sales [4]. The industry also maintains the highest research spend as percentage of revenues versus any other industrial sector. For example, the pharmaceutical industry in USA spent 67.4 billion dollars in R&D during 2010, approximating 17% of its global sales [2011 Profile (2011), Pharmaceutical Research and Manufacturers of America (PhRMA); Washington DC; http://www.phrma.org/sites/default/files/159/phrma_profile_2011_final.pdf]. From a global perspective, the total R&D investment

E-mail address: ikhanna@kareustherapeutics.com.

for top 20 pharmaceutical companies amounted to 96 billion dollars. This is fairly high investment considering that only 20% of approved drugs make more money than the associated R&D cost [2011 Profile (2011), Pharmaceutical Research and Manufacturers of America (PhRMA); Washington DC; http://www.phrma.org/sites/default/files/159/phrma_profile_2011_final.pdf [5]].

Industry challenges

Despite large investments, the pharmaceutical industry has faced marked decline in productivity. The size of the company or R&D budget does not guarantee proportionate success. During decades, there have been several players (4300) in pharma sector but only a small subset (261) seem to have tasted success with at least one NME approved [1]. Currently, only 12% of these companies are in existence while the remaining 88% have disappeared from the scene or merged with other organizations. The discussion below captures a summary of challenges being faced by the industry.

High cost, high failure

Despite technological advancements and large R&D investments, the number of new drug applications (NMEs and NBEs) approved per year by FDA was the lowest (20–25 per year) during six years (2005–2010). Interestingly, one of the emerging trends during 2009 and 2010 has been a distinct shift from primary care blockbuster mindset to specialty products. Of the drugs approved in 2009 and 2010, 24% (six- and five-in respective years) belonged to orphan drugs and specialty care [2]. This trend has continued during fiscal 2011 wherein the drug approvals related to rare and/or orphan disease (total ten) contributed to making this as one of the most productive years during past decade with a total of 35 drug approvals by FDA [6,7]. Many experts, however, believe that total number of drug approvals per year may not rise dramatically during the coming two to five years at least for primary indications. This low approval rate is also compounded by rising drug development cost. By many estimates, the average cost of taking a drug from concept to market is in excess of US $1 billion dollars ($0.8–1.8 billions) when adjusted for post-approval Phase IV expenses and costs linked to approval in non-US markets [1]. These numbers have varied with the company size and the type of drug product under consideration. The smaller organizations and acute or subchronic indication products tend to have significantly lower development cost. In addition to the rising development costs, the discontinuations of several advanced molecules in late Phase II and Phase III have contributed to rising burden on R&D budgets.

Dissipating proprietary assets and diminishing pipelines

The blockbuster products with annual sales of ≥1 billion dollar identified in the decade of 1990s forced many companies to implement changes in R&D strategic thinking. To balance the risk–reward ratio, many large companies could not justify investing in products with lower or moderate market size (<300 million dollars) potential. Unfortunately, the strategy has not worked well in general. The product pipeline in industry is starving; eagerly awaiting enrichment with quality products. In addition, many matured products that contributed to the sustenance and growth

of pharmaceutical companies are losing proprietary protection. In this regard, the era of 2009–2014 is anticipated to be the worst for proprietary pharmaceutical history contributing to 209 billion dollars erosion from its revenues with impending patent expiry. Many companies have been struggling to fill the gaps or compensate for the projected evaporation of revenues. During the past few years, there has also been emergence of life-threatening side effects with some established products after several years in market and exposure to millions of patients worldwide. This has forced regulatory agencies to withdraw these products from market and adopt stringent approval guidelines. New protocols for tracking safety and defining efficacy of marketed drugs have been implemented. In many cases such as in drugs for cardiovascular and diabetic patients, FDA is enforcing extended trials including cardiovascular events outcome studies to prove efficacy and long-term safety before drug approval. Many drugs based on new mechanism are also required to conduct additional studies or monitor safety parameters post-approval.

The diminishing pipelines and anticipated loss of revenues from expiry of patented life is shifting many companies from 'thriving' to 'surviving' mode. The whole sector, particularly large companies, has been making frantic efforts to reduce expenses and find viable options to substitute expiring blockbuster products. During past five years, the top ten pharma companies have eliminated more than 200,000 jobs. The mergers and mega-mergers followed by elimination of redundant functions have emerged as a norm. The trend is anticipated to continue in coming years leaving large pool of qualified scientists struggling to sustain. These measures have helped curtail expenses in short term but the changes have not helped spark productivity [8].

Globalization and shifting research

With rising drug discovery cost, the industry has been exploring avenues to get optimal value from R&D budget. Both China and India have large talent pool and are offering breadth of preclinical and clinical services at significant savings of 30–80% versus the cost in the USA. Many large pharma companies and global contract research organizations (CROs) have set up or are trying to create research centers in China, India and Singapore. These countries are maturing rapidly in competitive skills needed in various facets of pharmaceutical R&D. Some companies in China and India are also investing in R&D, although largely in risk-shared collaboration models. With signing of patent treaty, these markets are escalating with new partnering and business deals in R&D, manufacturing, clinical trials and marketing.

Socio-economic and political climate

The health care costs are spiraling globally and there is increasing debate within pharma sector to address challenges. In addition, the 'baby-boomers' and global population are aging. The US Census Bureau estimates that approximately 12.9% of US population was above 65 years age in 2009 which is likely to grow in coming years. With aging population, the health care cost and demands on price-control of drug products are expected to escalate. The socio-economic demands and high failures is forcing pharma industry to reassess R&D strategies and improve efficiency and productivity.

Reviews • KEYNOTE REVIEW

Low productivity analysis

The low productivity and rising R&D costs is forcing companies to evaluate reasons and modify course. The segment below dissects different factors contributing to low productivity.

Clinical failures – shifting paradigm

The trend in drug failures has changed during the past 20 years. The comparison of clinical attrition trends between 1991 and 2000 indicates that the principal component of drug failure in 1991 was unacceptable pharmacokinetics profile in human [9]. Since then, the industry has adopted several preclinical screens to address permeability, metabolism, distribution and excretion issues including allometric scaling for projection of human pharmacokinetics profile. The efforts have clearly paid off (Fig. 1), demonstrating marked improvement in success rates on drug metabolism and pharmacokinetics (DMPK) issues during 2000. This progress has continued since with regular delivery of improved DMPK candidates from preclinical pipeline.

Recently published reports by the Center of Medical Research (CMR) analyzed the reasons for drug failures in Phase II and Phase III during recent past. Analysis of the failure data from 16 pharmaceutical companies (accounting for ∼60% of global R&D spend) suggested that Phase II was the most vulnerable phase and exhibited the highest attrition of all phases. It is disappointing to observe that the success rate in Phase II from these companies fell down to 18% during 2008 and 2009, even lower than 28% recorded in 2006 and 2007. Thomas Reuters Life Science Consulting analyzed the drugs for major indications that were dropped in Phase II during 2008–2010 and for which the reasons for failure were disclosed (87 out of 108) [10–12]. The analysis (Fig. 2) indicated insufficient efficacy to be the foremost reason (51%). The failure due to strategic reasons (29%) also accounted for high attrition; possibly linked to lack of discrimination (versus competition) or insufficient risk/benefit ratio. Approximately 19% of investigational drugs fell owing to safety concerns or non-

sufficient margins. Many of the failed candidates belonged to peroxisome proliferator activated receptor-gamma (PPARγ) and factor Xa targets for which the expectations had been raised high during the past years. Approximately 68% of these failures seem to belong to metabolic, cardiovascular, cancer and neuroscience [13].

Similarly, analysis of Phase III submissions during 2007–2010 by CMR, indicated approximately 50% overall failure rate for drugs for the primary or major new indications (Fig. 2). The formulation changes or close extensions of previously approved drugs were excluded from this analysis. The lack of efficacy (66%) was again the overriding reason for investigational drug failure. The safety concerns and lack of risk/benefit ratio emerged as the second reason and contributed to failure of 21% candidates. The efficacy failures were attributed to non-significant improvement over placebo (32%), lack of discrimination versus control (5%) and lack of benefit as an add on therapy (29%). The novel mechanisms and unmet medical needs in cancer and neurodegenerative diseases accounted for a large number of these failures. Many of the failures seem to be linked to clinical exploration of life extension strategies, particularly in cancer, where compounds with success in one tumor type gave poor outcomes in other tumor types [14]. The average combined time for clinical and approval phase for new drugs increased to 95 months during 2000s relative to 77 months for new drugs in 1990s [Tufts center for the study of drug development, http://csdd.tufts.edu/news/complete_story/pr_ir_may-jne_2011]. Added to preclinical stage timeframe, this amounts to >12 years from project initiation to market leaving proprietary patent life to approximately ten years.

Incorporating success rates observed at various clinical phases, Fig. 3 shows the 2010 productivity trend and percentage of molecules surviving at each clinical phase. The drug discovery productivity (∼6%) during 2009 and 2010 seems to be one of the lowest in pharmaceutical history. The rate of success would give better numbers if close extensions of previously approved drugs were included in this analysis. The trend, however, is alarming and
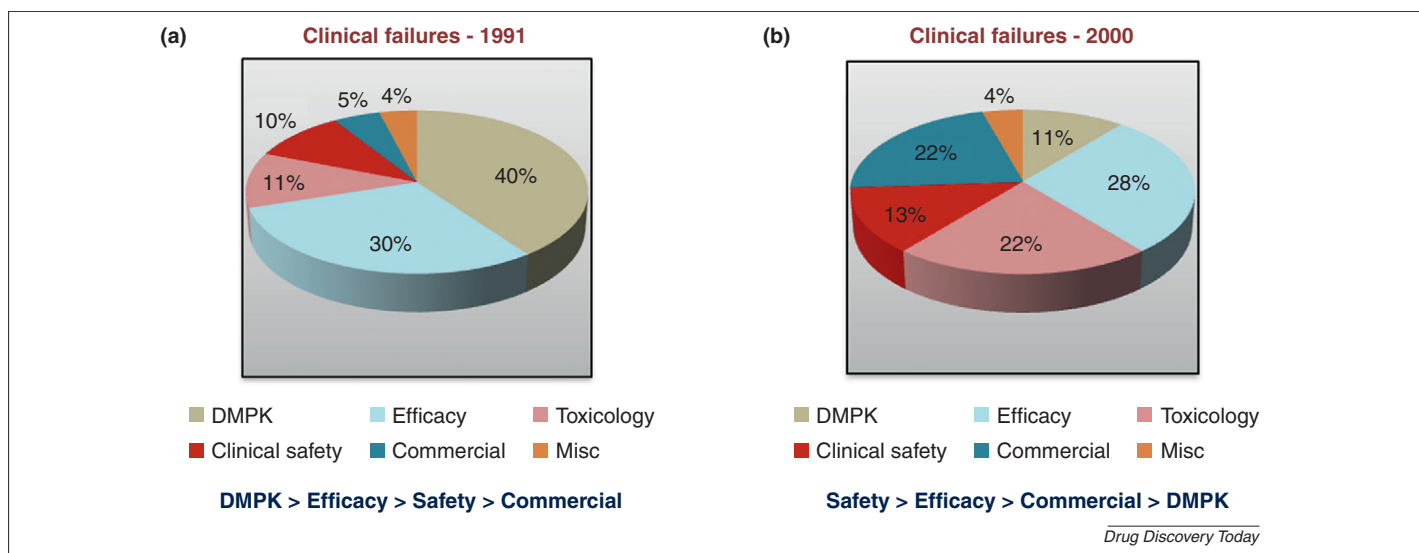

(a) Clinical failures - 1991

- DMPK — 40%
- Efficacy — 30%
- Toxicology — 11%
- Clinical safety — 10%
- Commercial — 5%
- Misc — 4%

DMPK > Efficacy > Safety > Commercial

(b) Clinical failures - 2000

- DMPK — 11%
- Efficacy — 28%
- Toxicology — 22%
- Clinical safety — 13%
- Commercial — 22%
- Misc — 4%

Safety > Efficacy > Commercial > DMPK

Drug Discovery Today

FIGURE 1

Shifting paradigm in drug failures during the past two decades. The clinical phase (I–III) failure of drugs is divided based on reasons of failure in the years 1991 **(a)** and 2000 **(b)**. *Abbreviation*: DMPK: drug metabolism and pharmacokinetics.
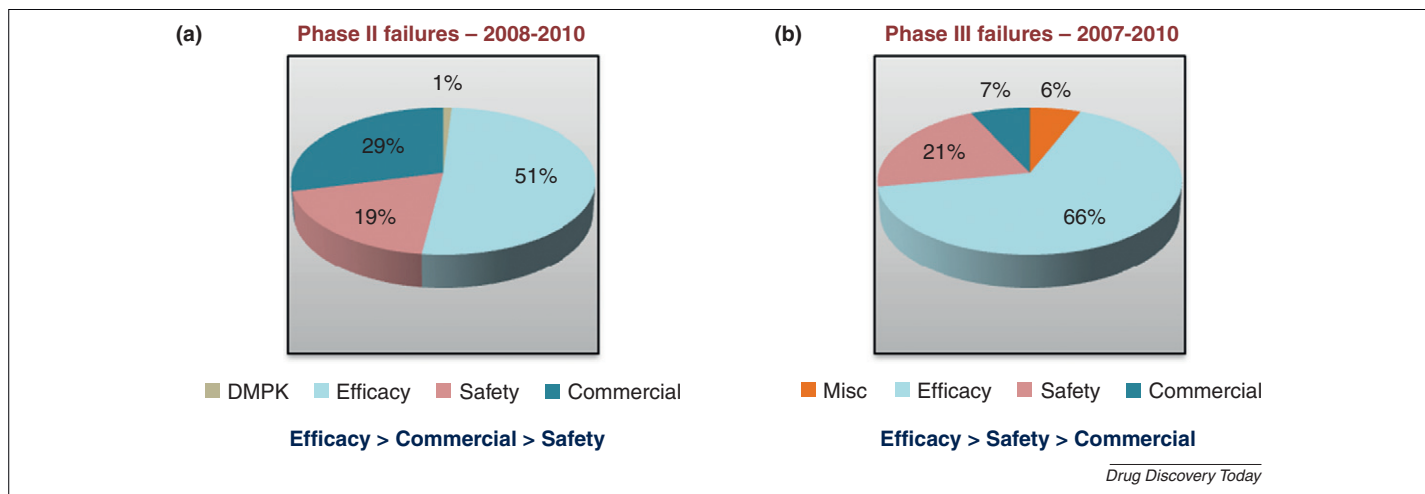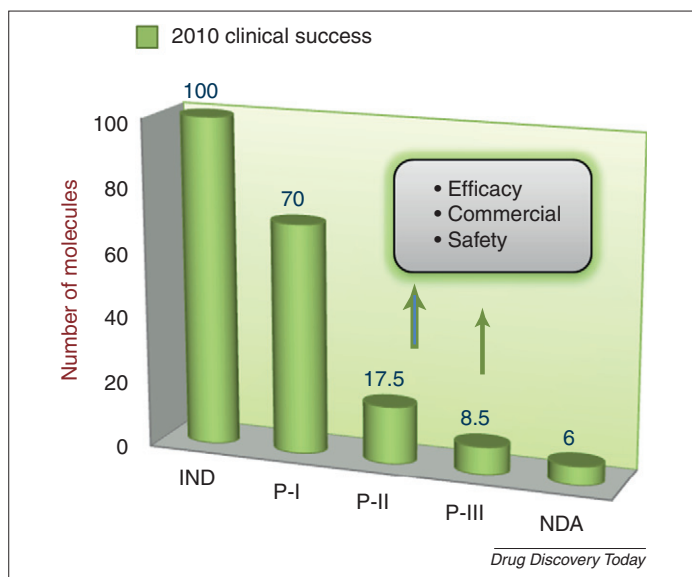
FIGURE 2

Emerging trends in late phase drug failures. The Phase II failure of 87 drugs **(a)** during the years 2008–2010 and Phase III failure of 83 drugs **(b)** during the years 2007–2010 are divided based on reasons of failure. *Abbreviation*: DMPK: drug metabolism and pharmacokinetics.

grabs attention. The weakest links relate to non-optimal efficacy, non-discriminatory profile versus competition and clinical safety issues.

To understand the reasons for insufficient efficacy, let us look at the disease modulation approaches investigated. Since the discovery of the human genome, extensive work has been done to identify useful targets that play a role in human diseases. Despite early anticipations, useful targets available for disease interception have remained fairly low. The research has helped validate some of these targets in disease states and a select few have exhibited success in clinic. By the same token, a large number of drug molecules based on target centric approaches have failed to yield desirable outcomes in humans. These failures have generally been attributed to safety issues or lack of optimal efficacy possibly

because of non-critical role of target or triggering of physiological compensatory mechanism during partial dysfunction. In a recent publication, Swinney *et al*. analyzed the origin of small molecule NMEs approved during the ten years (1999–2008) [15]. Interestingly, of the 78 drugs (NMEs and NBEs) approved with first in class, novel mechanism, the majority (28; 37%) were based on phenotypic screening approaches in comparison to drug approvals (17; 23%) based on target-based screen. By contrast, for follow-on drugs a majority of small molecule NMEs approved (164) emerged from target screen (83; 51%) versus phenotypic assays (30; 18%). The phenotypic screen seemed to be more fruitful in CNS and infectious diseases whereas target-based screen appeared to be more successful in oncology. Historically, much before the advent of target linked genomic era, phenotypical screening approaches were the preferred way to discover new medicines. Both of these approaches have their advantages and disadvantages and one-size may not fit all. By contrast, all the NBEs were discovered through target-based screen. The higher success of target-based approach in follow-on projects indicates the speed and efficiency at which competition can catch up with first in class molecules. By many estimates, the time for market exclusivity for first in class drugs is shrinking and is averaging at approximately 1.2 years compared with approximately ten years exclusivity witnessed in the 1970s.

In addition to the inadequate clinical efficacy, lack of competitive differentiation and safety concerns continue to be the paramount reasons for drug failure during advanced phases. These failures could be linked to incomplete understanding of the human diseases and mechanisms investigated, lack of correlation of animal models to human diseases, poor biomarkers and surrogate endpoints, selection of non-optimal drug molecules (pharmacokinetics/pharmacodynamics profile, off-target effects, among others), idiosyncratic drug toxicity and poor clinical trials design.

FIGURE 3

Productivity trend during 2009 and 2010. The clinical rate of success is depicted as percentage surviving at each clinical phase based on attrition observed during 2009 and 2010.

Non-technical factors in low productivity

The success rate in drug discovery has been low at both the small and the large companies. The innovation decline in many large pharma may be linked to several factors, including regimented

systems, corporate culture, mergers, uncertainty and lack of commitment to long-term vision. Many project leaders are driven to accomplish immediate project goals and timelines and push for advancing molecules to clinic, even when profile is not optimal.

Small biotech companies are recognized as innovation driven centers with low bureaucracy and higher flexibility. These companies generally exhibit higher ownership and stronger commitment to research mission but tend to be cash starved and are swayed by cost–benefit ratio before undertaking any study. Detailed investigation in lead optimization is avoided with restrained funds. The fear of failure looms large at times and critical experiments that can potentially kill the projects are avoided. The typical life span of many start-up biotech companies ranges between three and five years during which these companies either enter growth, licensing phase or fold down. The pressure of survival and timelines, forces some companies to compromise quality and advance non-optimal compounds to clinic with higher risk.

The disconnect between business and research goals can also lead to non-productive outcomes and unhealthy relationships. This is particularly important for small- to mid-sized companies. Shifting policies and unclear vision can only create unrealistic expectations and unhealthy research environment.

Improving productivity and probability of success

The pharmaceutical companies are going through realignment to improve efficiency and increase output. The low R&D productivity is not sustainable and several models are being adopted and debated to improve output in a cost-effective way [16]. The data in Fig. 2 indicates that ≥70% failures in Phase II are related to technical deficiencies whereas approximately 29% may be related to non-technical (strategic, commercial, among others) attributes. The discussion below summarizes avenues to enhance probability of success in preclinical and clinical phases. This segment is followed by detailed discussions on innovation driven collaboration models, creating balanced portfolio and stimulating research culture to enhance productivity.

Preclinical efficiency

Preclinical efficiency can be enhanced by creating strong validation data on therapeutic approach in addition to strengthening safety and product differentiation profile. The discussion below offers elaboration.

Disease modulation

The target selection or disease modulation approach is the first critical step in the process and lays foundation for the success or failure of project. It, therefore, becomes vital to build strong validation of the approach and define its limitations. The academic centers and small biotech companies continue to be the fertile grounds of innovation. Highly selective, target-based approaches have yielded several successful medicines. The target centric approaches are desirable because these complement well with high-throughput screens and give meaningful structure–activity correlations in lead optimization phase. However, there are shortcomings of the approach as well. The inadequate efficacy and/or non-optimal safety have emerged as limitations during clinical investigation in some instances. The binding or interaction of a potential drug molecule on a target may trigger complex

response mediated through interconnected network biology, which may compensate, enhance or negate the initial event. Many believe that most chronic diseases are multifactorial disorders and modulation of a single target may not yield an optimal response. The analysis of tissue and plasma samples from disease population can help validate target hypothesis. For many diseases, it may be beneficial to aim broader phenotypic or pathway modulation approaches [15,17]. This is particularly relevant for complex, chronic diseases where the disease understanding and therapeutic approaches are in evolutionary phase. One of the advantages of the phenotypic screening is that no prior understanding of the mechanism is needed as the screening assays can be designed to give good functional read out. However, low-throughput and lead optimization difficulties in generating good structure–activity relationships create challenges. Both these approaches have their merits and should be investigated in preclinical exploratory phase to compare and narrow down the preferred choices. Recognizing it as a crucial step for the project, several innovative collaboration models are emerging to address the issues. These include public–private partnerships, open innovation models, and industry–academic partnerships The public–private partnerships, such as IMI, Arch2POC, National Center for Advancing Translational Sciences (NCATS), Cancer Therapy Evaluation Program (CTEP), Dundee Kinase Consortium, summarized in Table 1, work in a non-compete framework to understand and attack disease with collective wisdom. Similarly large pharma is looking beyond territories in 'open innovation' model (Table 2), inviting grant proposals from scientists in academic or biotech world for novel targets validation and early discovery phase collaborations. Some of these include – 'Grants4Targets' by Bayer, 'Call for Targets' by MRC Technologies 'Phenotypic Drug Discovery Scheme' by Eli Lilly or 'Pharma in Partnership Program' by GSK, the Incubator Concept by Biogen Idec, 'Center of Excellence for External Drug Discovery' as virtual pharma discovery at GSK. Apart from these initiatives, grants from government agencies, charitable trusts and foundations (Table 1) continue to provide very useful avenues for conducting fundamental research in disease states and early discovery phase.

Animal models

Relevant animal models with good correlation to human diseases are crucial for compound evaluation and comparative analysis. This continues to be a hurdle for many diseases. The animal models pertinent to specific mechanism of action may need to be developed to validate mechanistic hypothesis in preclinical phase but translation of these models to progressive human diseases remains an independent and at times insurmountable challenge. For some acute indications such as in antimicrobial therapies, animal models show fairly good translation to human diseases. But for chronic diseases, long-term disease models and appropriate second species models that validate mechanism with relevant biomarkers and/or imaging technologies and show clear evidence of disease modulation would be important in building confidence and improving probability of success.

Idiosyncratic toxicity

The preclinical screens (herg, genotox, target selectivity, in vivo safety pharmacology in multispecies) have helped identify improved quality of molecules entering the clinic. The idiosyncratic drug toxicities particularly observed on chronic use (e.g.

TABLE 1

Precompetitive public–private partnerships for innovative drug discovery

Consortium or Partnership	Collaborators and scope
National Center for Advancing Translational Sciences (NCATS)	• NIH supported; launched in 2012. Formed primarily by uniting and realigning existing NIH programs that have key roles in translational science. Working in partnership with the public and private sectors • Generate innovative methods and technologies that will enhance development, testing and implementation of diagnostics and therapeutics across wide range of diseases • Early emphasis on drug repurposing; discontinued molecules from pharma partners • http://ncats.nih.gov/index.htm
Innovative Medicines Initiative (IMI)	• Largest public–private partnership; established to improve competitiveness of pharma sector in Europe. Founding members European federation of pharma industries (EFPIA) and European commission (EC) • Two billion pounds budget; launched in 2008 • Development of tools and methods to predict efficacy, safety and knowledge management system • http://www.imi.europa.eu/
Dundee Kinase Consortium	• University of Dundee and large pharma partnership to explore new approaches to treat diabetes, cancer and arthritis. Operational since 1998 • Generate largest collection of drug targets, know how related to protein kinases and phosphatases • http://www.biodundee.co.uk
Arch2POCM	• Public–private partnership – academic, pharma industry, regulatory scientists, clinicians, public and private funders and patient groups. Launch anticipated 2012 • Validate novel, high risk targets together in open access framework. Initial focus on cancer, autism and schizophrenia • Collectively owned; advance investigational molecules as far as POC Phase II. Pharma can buy exclusive rights to data generated from successful unpatented drug or, use the research in own proprietary research • http://www.sagebase.org/partners/Arch2POCM.php
Enlight Biosciences	• Partnership between six large pharma and venture capitalist Pure Tech Venture; founded in 2008 • Develop platform technologies that could be basis for stand alone companies. Spun off Entrega in 2011 to develop oral delivery of biologic drugs • http://www.enlightbio.com/
Structural Genomics Consortium	• Non-profit organization funded by Canada, GSK, Merck, Novartis, Knut and Alice Foundation, Wellcome Trust. Established since 2003 • Determine 3D structures of proteins of medical relevance for public use without restrictions • http://www.sgc.utoronto.ca/
SNP Consortium	• Consortium of pharma industry, bioinformatics and academic centers, and Welcome Trust. Launched in 1999 • Develop and freely distribute high density map of human SNP • http://genome.gov/100053; http://snp.cshl.org/; http://www.sanger.ac.uk/HGP/Poly/snp
Cancer Therapy Evaluation Program (CTEP)	• NCI supported • New treatments for cancer; understanding cancer • http://ctep.cancer.gov/default.htm
Coalition Against Major Diseases (CAMD)	• Consortium of pharma industry, global regulatory agencies, patient advocacy groups, research foundations, academia, scientific associations, and consultant groups. NCI supported • Create common data sharing standards to facilitate faster review by FDA and global regulatory agencies • Establish databases of standardized pharmaceutical clinical trial data as a tool to design more efficient clinical trials of new treatments • Develop disease progression models to aid clinical trials • Identify biomarkers for clinical trials • http://www.c-path.org/CAMD.cfm
Alzheimer's Disease Neuroimaging Initiative (ADNI)	• Consortium of pharma industry, National institute of aging, National Institute of bioimaging and bioengineering. Initiated in 2004 • Define rate of progression of mild cognitive impairment and Alzheimer's disease • Develop improved methods (biomarkers, imaging) for clinical trials in Alzheimers • Public access to clinical and imaging data • http://www.adni-info.org/
Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium	• Public–private biomedical research partnership; FNIH managed • Discover, develop, and qualify biomarkers to support new drug development, preventive medicine, and medical diagnostics • Development of biomarker-based technologies, medicines, and therapies for the prevention, early detection, diagnosis, and treatment of disease • http://www.biomarkersconsortium.org/
Foundation, Trust	*Collaboration scope*
Seeding Drug Discovery Initiative	• Wellcome Trust • Develop drug-like, small molecules for lead optimization by biotech and pharma industry in areas of unmet medical need

TABLE 1 (*Continued*)

Foundation, Trust	Collaboration scope
	• http://www.wellcome.ac.uk/
Medical Research Council Development Pathway Funding Scheme	• Basic and translational research • Preclinical and early clinical testing of novel therapeutics, devices and diagnostics, including 'repurposing' of existing therapies. http://www.mrc.ac.uk/Fundingopportunities/Grants/DPFS/index.htm
Gates Foundation	• TB, malaria, HIV • http://www.gatesfoundation.org/
Gates Foundation	• Consortium in collaboration with 13 large pharmaceutical, $785 M fund • Eradicate ten long-neglected tropical diseases by 2020 • http://www.bloomberg.com/news/2012-01-30/drugmakers-join-gates-foundation-in-fighting-tropical-diseases.html
Drugs for Neglected Diseases	• Develop new treatments for neglected diseases such as trypanosomiasis, leishmaniasis, chagas, malaria • http://www.dndi.org/
Fox Foundation	• Develop novel treatments for Parkinson's disease • http://www.michaeljfox.org/

TABLE 2

Crowd Sourcing; open innovation in drug discovery

Partnership	Collaboration scope
Grants4Targets	• Bayer sponsored • Grants for Target ID, validation in oncology, gynecology, cardiology, and hematology • Joint collaboration on moving from target validation to drug discovery http://www.grants4targets.com
Call for Targets	• MRC Technology sponsored • Basic research on therapeutic antibody targets • http://www.callfortargets.org/
Phenotypic Drug Discovery (PD2)	• Lilly sponsored • Screening of external molecules in phenotypic modules to identify compounds of potential therapeutic utility; possible collaboration with compounds of mutual interest • http://www.pd2.lilly.com
Target Drug Discovery (TD2)	• Lilly sponsored • Screening of external molecules in target-based assays to identify compounds of potential therapeutic utility; possible collaboration with compounds of mutual interest • https://openinnovation.lilly.com/
InnoCentive	• Open innovation company started with seed money from Lilly; spun out of Lilly in 2005 • Connects companies with research challenges to external solution providers who receive prize for offering solutions • https://www.innocentive.com/
YourEncore	• Open innovation company; being used by Lilly and P&G • Uses a large network of retired and veteran scientists who serve as paid experts to help companies during various stages of R&D issues • http://www.yourencore.com/
CTSA portal	• Open initiative • Industry and academia collaboration in drug repositioning • http://www.ctsapharmaportal.org/
NCGC-NPC browser	• NIH Chemical genomic center (NCGC)–pharmaceutical collection (NPC); open initiative • Comprehensive, publically accessible collection of approved and investigational drugs for HTS for validating new disease models and identifying new treatment options • http://tripod.nih.gov/npc/
Fully Integrated Pharmaceutical Network (FIPNet)	• Lilly sponsored • Seeks ideas, resources and talent beyond walls through collaboration with external scientists, academic and biotech firms
Pharma in Partnership (PiP) Program	• GSK sponsored partnership with academics • Exploration of novel ideas for therapeutic utility • Exploration of novel agents/candidates for further development • http://www.pharmainpartnership.gsk.com
Center of Excellence for External Drug Discovery (CEEDD)	• GSK sponsored; Virtual company • Promotes drug discovery through external innovation Risk reward shared collaboration • http://www.ceedd.com

TABLE 2 (Continued)

Partnership	Collaboration scope
Biogen Idec Innovation Incubator (Bi3)	• Biogen Idec sponsored • Provides funds, infrastructure and strategic support for entrepreneurial scientists on novel biologic ideas for therapeutic utility • http://www.bi3.biogenidec.com
Strategic IP Insight Platform (SIPP)	• IBM initiated; donated to NIH. open access • IBM used pharmaceutical data from BMS, AstraZeneca, DuPont, Pfizer • Data extracted from 2.4 million compounds, 4.7 million patents and 11 million biomedical journals • Researchers at the NIH are expected to use the information to discover new medication and research cures for cancer

tumor development, cardiovascular events) and late clinical phase trials are the most costly and hurtful. The selection of appropriate biomarkers or surrogate endpoints that can build confidence on safety of target or rule out any 'off-target' effects observed in preclinical screens can help eliminate less promising candidates early.

Quality rather than quantity

Many in industry believe that larger the size of clinical pipeline, higher the chances of success even after factoring in standard attrition. The scientists and project teams work aggressively to enrich pipelines within projected timelines. When the quality of leads is compromised the cycle gets viciously intense and organizational pressure mounts as non-optimal candidates fall from clinic. The history suggests the quality candidates may start with some lag versus competition but can catch up and win over non-optimal candidates in the race. The extra time spent in generating a quality lead contributes to steady progression in later phases. This is particularly important for small biotech companies that struggle with time, budget and constant demands to demonstrate progress. The clinical candidate(s) once selected cannot be reversed; and the small companies may not get more than one chance to test hypothesis. The failure can also tarnish the target or pathway approach prematurely. Most companies start with larger basket of projects in exploratory phase (preclinical) and utilize filtration funnel to rapidly eliminate projects that do not meet pre-established criteria. The efficiency of process and quality of lead generated can be improved by judicious selection of available technologies at various stages of drug discovery such as target ID and/or validation (over expression and knockout), hit generation phase (X-ray crystallography, structure guided drug discovery (SGDD), fragment based, virtual screening, high throughput screening (HTS)) to lead optimization (scaffold hopping, allosteric versus active site modulation, drug pharmacokinetics properties such as absorption, distribution, metabolism and excretion (ADME), selectivity and safety screens) [18–20], The projects in lead optimization and clinical phase should always have 'critical killer' experiments with intent to substantiate the 'target product profile' and establish discrimination versus standard of care or competing molecules in clinic. The innovation is crucial in lead generation and for problem solving along the way. The quality of molecules including their pharmacokinetic and/or pharmacodynamic correlation, ADMET profile and good therapeutic index are important for projection of human profile. It is also important to maintain some discovery efforts after advancing candidates to the development phase, if the organization believes in the approach. The persistence can

help identify second generation candidates with an improved profile.

Innovative clinical investigation

The clinical studies of molecules must be designed with goal to assess critical efficacy and safety parameters as early as possible in a cost-effective manner. The study design should consider patient stratification strategies, computational simulation models, biomarkers, imaging, scoring systems or surrogate endpoints to evaluate the potential of the drug molecule. Many companies are adopting innovative 'quick win, fast fail' strategies [16] to reach go/no go decision on clinical molecules as early as possible. Lilly has implemented 'Chorus' as a new model for quick, cost-effective, clinical proof-of-concept [21]. The 'Coalition Against Major Diseases' made up of government agencies, pharmaceutical companies, and patient advocacy groups has developed standardized clinical trials database that enables researchers to design more efficient studies for new treatments, initially for Alzheimer's and Parkinson's diseases (Table 1). In addition to the techniques discussed, the microdosing (Phase 0) can be useful in select cases to prioritize compounds and get an early assessment of human pharmacokinetics profile. Using microdose of radiolabeled investigational drug at 1/100th predicted therapeutic dose, in combination with positron emission tomography (PET), can help get an early assessment of human pharmacokinetics profile and targeted tissue distribution (brain, tumor, among others). The microdosing approach assumes linearity in the pharmacokinetics profile during dose scaling but can yield useful early information in a cost-effective manner with low compound needs.

Symbiotic model of innovation

With access to a strong talent pool, and modern technologies, the large pharma has demonstrated good success with validated targets as approximately 70% of NMEs approved during 1998–2007 based on follow-on approaches, originated there [22]. The large companies have, however, been much less successful in novel treatment options for the primary and secondary diseases. For example, ≥50% NMEs based on novel mechanisms and approximately 70% orphan drugs, approved between 1998 and 2007, originated at small biotech or universities [22]. The continued low productivity and complexity of chronic diseases is stimulating large pharmaceutical companies to look beyond the traditional model of home grown research and explore external alliances to fill innovation gaps.

The times have changed in the academic world too. Traditionally, the academic research centers favored working independently

generating ideas and validating hypothesis with grant funds obtained from government agencies, foundations, trusts or industry sponsored research. When the research yielded data of commercial interest, the technology and assets were out licensed to industry which evaluated the druggability and merit of the approach. The academic institutes and industry worked independently ensuring non-interference in each other's expertise and arena. Over time, the academics have contributed immensely to developing better understanding of the complex disease states and identifying novel pathways for disease intervention. By contrast, the academics have generally not been as strong in ranking druggability of targets, identifying practical hits or being sensitive to intellectual property protection. This has changed during the past decade. The funds available from government or private agencies seem to be diminishing and the academic world is looking to industry for support in fundamental research and identifying areas of mutual interest. The regular interactions with industry are making academic institutes increasingly cognizant of the industry needs. Many of these partnerships are beginning to yield rewards. For example, TNF-α antibody work originating at Kennedy Institute, Imperial College and Cambridge Antibody Technology has been converted to blockbuster products (etanercept, infliximab and adalimumab) for rheumatoid arthritis through industry participation [23]. Many academic institutes such as Imperial Innovations (http://www.imperialinnovations. co.uk), Medical Research Council Technology (http:// www.mrctechnology.org), Broad Institute (http://www.broad.-mit.edu) are building entrepreneurial arms either alone or in conglomeration with other institutes to generate constant stream of revenues through fee for service (CRO) for use of specialized technologies; or by out licensing validated concepts and intellectual property to biotech or large pharma industry.

The small biotech companies are also brewing grounds of innovation and have been credited with several drug approvals based on novel mechanism for primary indications or orphan diseases [22]. The small biotechs are, however, cash and resources starved in early phases and typically participate in risk shared partnerships with pharma and academic institutes to optimize and advance projects.

Because of persistent financial strain in biotech and academic sectors, and continuing low output at large pharma industry, the time and the need seem ripe for building co-operation bridges to fill innovation and skill gaps and improve probability of success in drug development. For example, to address high clinical failures associated with inadequate efficacy, the large pharma is looking to academic research centers and small biotechs to identify druggable approaches. The academic institutes and small biotech companies generate novel ideas and early hits whereas large pharma collaborations help develop these hits into drugs. The industry–academic marriage has seen good success in validating new targets and realizing novel treatments for unmet diseases. Several risk and technology shared partnering initiatives between academic institutes, specialty biotechs, and large pharma have materialized during the past few years. These can broadly be classified as (i) precompetitive collaborations; (ii) open research models, (iii) pharma industry (large and/ or biotech)-academic collaborations encompassing early phase discovery to proof of relevance in clinic and (iv) venture funds

to support drug discovery from idea generation to new drug application (NDA) approval.

Precompetitive collaborations

Several partnering models comprising academic institutes, large and small pharma industry members are emerging with defined goals, for example, to develop better understanding of complex diseases; identify and validate new targets or therapeutic approaches; develop tools, assays, methods for hit generation; seek and validate novel biomarkers for prediction of efficacy and safety. These partnerships get financial support through a range of public and private sources, such as government agencies, foundations, charitable trusts, pharmaceutical industry and academic institutes. The partners have open access to the data, technology and training options to utilize in their own research or proprietary projects. A brief account of select consortia and emerging partnership models, their scope and objectives is summarized (Table 1). For example, the Innovative Medicines Initiative (IMI) is the largest public–private partnership established to strengthen competitiveness of pharma sector in Europe [24]. The consortium comprising of European Federation of Pharma Industries (EFPIA) and European Commission (EC) aims to develop technologies and methods to predict efficacy and safety in complex diseases. Similarly, the Dundee Kinase Consortium (DKC) aims to build the largest kinase library and know how around protein kinases and phosphatases. The Arch2POCM and Enlight Biosciences utilize collective knowledge of partners to validate novel targets and follow it up to create a spin-off company or auction off licensable asset to partners. The Alzheimer's disease Neuroimaging Initiative (ADNI) is developing biomarkers and imaging techniques to predict disease progression and to use methods in evaluation of NMEs in clinical trials. Similarly Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium aims to discover, develop, and qualify biomarkers to support new drug development, preventive medicines, and medical diagnostics in broad therapeutic areas. The NCATS and CTEP seek new treatment options for neglected diseases, and cancer through NCI–industry partnership. Despite several benefits outlined above and their marked contributions to advancement of science, the public–private partnerships are not without challenges. Some of these include complexity in project management with increasing size of partners, handling of intellectual property, performance and reward system, overlapping goals with other consortia and priority setting.

In addition to consortia and partnerships discussed, new initiatives are being implemented to encourage innovation [25,26]. For example, several foundations and government bodies, such as Wellcome Trust's Seeding Drug Discovery Initiative, EU Innovative Medicines Initiative for Basic and Translational Research, Bill and Melinda Gates Foundation, Fox Foundation and several other consortia and funds are available (Table 1 for select funds) to promote basic research and bridge the translational gap [26]. The academic collaboration on novel treatments encompass the breadth that includes primary care, orphan diseases, neglected or rare diseases and identification of new uses for existing drugs.

Open innovation

The pharma industry is also experimenting with open innovation or 'crowdsourcing' models made popular in the IT industry. The

model attempts to leverage collective expertise of a network of external scientists (the crowd) to identify new ideas or seek solutions to technical problems (Table 2 for select examples). Lilly has been part of several open innovation projects, including Inno-Centive, Your Encore, PD2 (phenotype drug discovery initiative), TD2 (target drug discovery initiative). The first two are web based solution providers – InnoCentive initiated with seed money from Lilly, connects companies facing research challenges to external solution providers who receive prize money for offering solutions. Similarly, YourEncore, an open innovation company, uses a large network of retired and veteran scientists who serve as paid experts to help companies during various stages of R&D issues. In a separate model, GSK is releasing 15,000 anti-malarial NMEs to academic institutes for probing new uses. Many other institutes are trying to establish portals (e.g. CTSA portal; NCGC-NPC browser) with goal to make the discontinued clinical molecules and the compounds from large library, easily accessible to participating partners and academic institutes for potential utility in new indications. As discussed earlier, many open innovation initiatives directed at exploring novel approaches, such as Grants4Targets, Call for Targets, Incubator Concept, Pharma in Partnership (PiP) are also available to the public for validating new ideas and participating in drug development (Table 2). Apart from crowd sourcing models, open partnering models, such as Fully Integrated Pharmaceutical Network (FIPNet) at Lilly, PiP Program and Center of Excellence for External Drug Discovery (CEEDD) at GSK and incubation model Biogen Idec Innovation Incubator (Bi3) offer attractive options. Many of these collaborative initiatives are proving useful but most seem to be confined to early or exploratory phase of drug discovery. The issues with intellectual property ownership and reward system continue to be a bit complex and challenging.

Large pharma–biotech–academic collaborations

With increasing interest in biologics, the academic-industry collaboration is also venturing in this arena aggressively (Table 3; for select partnerships). For example, Pfizer has established 'Centers for Therapeutic Innovation (CTI)' as open innovation partnering models with universities and hospitals to identify novel biologic therapeutics for unmet needs. The entrepreneurial partnering spans the range from early research through human proof-of-concept and Pfizer is committing >300 M investment during five years and establishing research centers in close vicinity of academic institutes to ensure optimal interactions. Similarly, GSK and Astra have joined hands with University of Manchester to establish Manchester Center for Inflamm Res (MCIR) with the goal to translate basic research into new medicines for inflammatory diseases. The collaboration of Sanofi Aventis with elite research institutes from France (Sanofi Aventis – AVIEASAN) attempts new treatment options in areas, such as aging, immunoinflammatory diseases, infectious diseases and regenerative medicine. Many other companies are also stitching similar collaboration with academic institutes or specialty biotechs [6,27]. During 2011, GSK announced plans to sign collaborations with ten academic centers for long-term discovery projects. Merck is investing $90 M over seven years in non-profit California Institute for Biomedical Research (Calibr) that aims to develop novel therapeutics in collaboration with academics around the globe. Merck will retain the first right of refusal on emerging molecules and targets with animal proof-of-concept, otherwise the institute keeps the rights to shop externally or spin-off a new company. Regulus, Gilead, Evotec, Elan and several other companies also announced plans to build strong ties with academic institutes during the year 2011. Overall, the collaborations between large pharma–biotech–academic are on the rise to mitigate risk and expand options on

TABLE 3

Industry–Academic partnership (select examples)

Partnership	Collaboration scope
GSK-Imperial College	● Alternate drug discovery initiative; new therapeutics for pain ● Established 2003
Astra – Imperial College	Cancer targets
Centers for Therapeutic Innovation (CTI)	● Open innovation partnering between Pfizer, universities and hospitals ● Identify novel biologic therapeutics for unmet needs ● Entrepreneurial partnering spans the range from early research through human proof of concept ● >300 M investment over five years http://www.pfizer.com/partnering/partnership_highlights/
Manchester Center for Inflamm Res (MCIR)	● Collaboration between GSK-Astra-University of Manchester ● Translating basic research into new medicines for inflammatory diseases
Sanofi Aventis – AVIEASAN	● Collaboration between Sanofi Aventis and French elite research institutes ● New research areas as aging, immunoinflammatory diseases, infectious diseases and regenerative medicine ● http://www.sanofi-aventis.com/binaries/20100217_Aviesan_en_tcm28-27394.pdf
Merck – VGTI-FL	● Collaboration between Merck and Vaccine and Gene Therapy Institute of Florida ● Discover and validate targets and pathways for HIV treatment ● Identify biomarkers for efficacy
California Institute for Biomedical Research (Calibr)	● Non-profit organization; Merck sponsored; $90 M plan over seven years ● Drug discovery collaboration between Calibr and academics around the globe ● Merck gets first right of refusal at animal proof of concept ● Otherwise can partner with other pharma or spin off as stand alone company ● http://www.merck.com/newsroom/news-release-archive/research-and-development/2012_0315.html

emerging drug candidates. It will be tough to summarize hundreds of collaborations emerging or executed and Table 3 illustrates select examples to give a flavor of emerging trends.

Many academic centers have built specialty wings using modern technologies (hit generation, SGDD, combinatorial libraries) to help small biotech companies with constrained capabilities. By contrast, specialty companies offer risk shared or fee for service collaboration options covering varied technologies and preclinical needs (such as drug delivery, ADME, safety screen, *in vivo* models, among others). In efforts to control cost and improve accessibility to technologies, many companies are collaborating with preferred CROs that offer broad or specialty skills and technologies for preclinical and clinical needs. For example, Lilly has established preferred CRO partnership with Albany Molecular Research Inc. (AMRI) and Covance for preclinical discovery and toxicology work. Similarly, utilization of cloud computing for data storage, retrieval and sharing information among designated partners is becoming popular. The Lily–Amazon partnership has generated elastic cloud (EC2) for data storage and sharing. Roche uses cloud computing for virtual screening. IBM has created a Strategic IP Insight Platform (SIPP) comprising of pharmaceutical data extracted from 2.4 million compounds, 4.7 million patents and 11 million biomedical journals and donated it to NIH for usage in anticancer research. Others companies, such as Wipro are building a clinical data management system to improve efficiency of clinical data handling and potentially reduce data processing and analysis time.

Another cost-effective, efficient, collaboration model that has seen increased popularity during past five years is a Virtual Company model. In this model, a core team sets strategic directions for the organization and utilizes preferred CROs to validate and advance projects to achieve targeted milestones. The advantages of no built in infrastructure cost, easy accessibility to global technologies, quick decision making, and flexibility in research prioritization makes the Virtual Company model fairly attractive. Eli Lily has established Chrous as an independent virtual company to establish rapid, cost-effective clinical proof-of-concept for internal and licensed molecules.

Venture funds options
With constrained micro economics, new creative deal structures and alliances are emerging with emphasis on partnering to share risk and rewards. Although innovation is a driver in deal making, interest in early collaborations seems to have intensified during the past two to three years. This is a marked shift from previous models wherein biotechs would carry projects to clinical proof-of-concept before partnering with larger companies. Early partnerships, equity holdings, option alliances with non-dilutive funding are emerging as desirable alternates. The risk shared deals (preclinical and clinical) with preferred partners are becoming common place. The early partnership as discussed in 'Symbiotic Innovation Model' is particularly relevant for novel mechanism based drugs (NMEs, NBEs) and benefits all partners. By contrast, partnering with large pharmaceutical on drug repositioning opportunities still tend to be postponed until establishment of clinical proof-of-concept. Detailed discussions on emerging models of deal structure are beyond scope of the article and have been addressed in other publications. Several funds catering to the stage and needs of the asset are available. The examples include invest-

ment funds that focus exclusively on pre-seed or idea generation phase (e.g. Biogeneration Ventures, Imperial Innovations), and funds that help advance early stage assets through proof-of-relevance [e.g. Atlas Venture, Forbion, Aretus (Virtual), Lilly-Mirror Fund, Third Rock, Velocity Pharma Development (VPD), Astra-Medimmune, Biopontis Alliance] or help late phase molecules through approval (Sofinova Ventures). The funds, such as Velocity Pharma Development acquire early stage assets and move these into virtual company with new management. With Lilly-Mirror fund, Lilly invests up to 20% capital, offers disease expertise and technical knowhow for rights to purchase back the successful molecules. This model is the basis of Astra-Medimmune fund also that invests in early biotech companies for rights to buy back. Biopontis Alliance is building network of University partners to develop licensable assets with potential to build preferred alliance with large pharma (Pfizer, Merck, and J&J) who can acquire assets after human proof-of-concept. It is clear that increasing numbers of large pharma companies have independent investment arms or are investing in venture funds with goals to expand their product generation options beyond home grown crop. The emphasis on 'collaborative' mode and tapping on external talent is certainly on the rise.

The all-encompassing 'Symbiotic Model of Innovation' addresses underlying issues in drug failure while attempting to fill gaps in current drug discovery processes (Fig. 4). The model highlights co-existence and helps partners tap on global expertise, cutting-edge technologies and varied skills efficiently throughout the drug discovery journey. The strengths and role of contributing partner at different phases of drug discovery are captured (Fig. 4). The model emphasizes innovation, utilizes strengths of each partner and is built to deliver quality drug candidates in a cost-effective manner. It is anticipated that variations of this model will likely be adopted rapidly in pharma industry during coming years.

Risk mitigated balanced portfolio
Apart from building partnerships to improve probability of success in primary indications as elaborated in 'Symbiotic model of innovation', the pharmaceutical companies are also trying to amend portfolio with less risky options that include life extensions in secondary indications, niche opportunities and combination products. Many branded products are being combined with other products to expand utility. The balanced portfolio may include the following options.

New molecular entities (NMEs)
The unprecedented approaches to drug discovery carry higher risk and a balanced portfolio should include a good blend of the first and the best in class molecules. Many in the industry prefer a ratio of about 30:70 for unprecedented to follow-on approaches in discovery portfolio. In addition, although blockbuster drug options remain viable, the inclusion of smaller market size opportunities can help reduce risk and improve organizational sustainability. The life cycle management opportunities comprising drug combinations, new drug delivery options, enantiomers, polymorphs among others, either alone or in partnerships, are becoming important part of the pharma strategies to maximize reward.

Novel biologics (NBEs)
The past decade has seen insurgence and large investments in biologics area. Approximately 30% of drugs approved during the
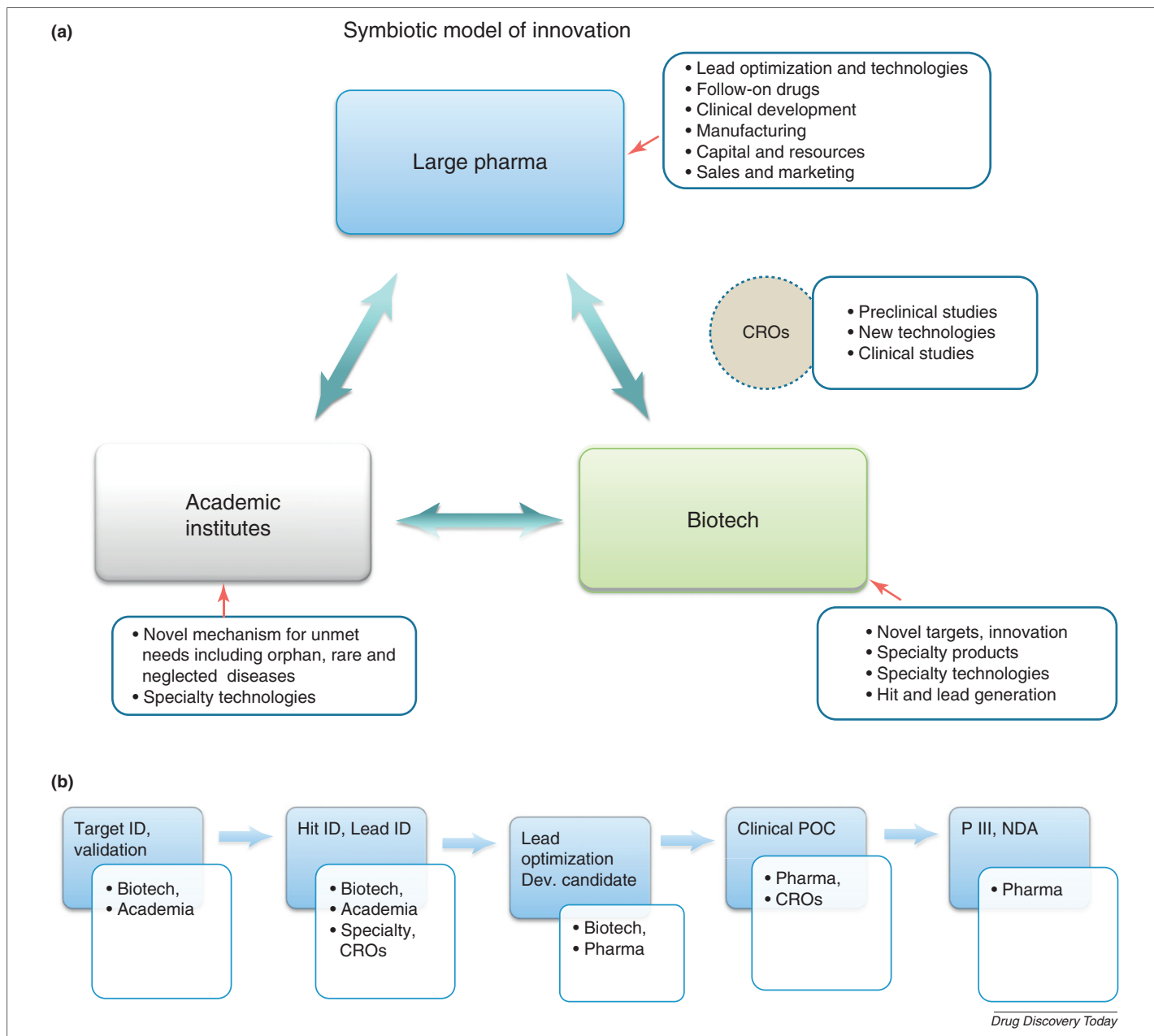
FIGURE 4

Drug discovery and critical partners. Core skills, strengths and capabilities at large pharma, small biotechs, and academic institutes are highlighted in boxes for building synergy in partnerships **(a)**. The capabilities at CROs are included to maximize partnership reward (a). Drug discovery progression path and centers of excellence are captured **(b)**. *Abbreviation*: CROs: contract research organizations; NDA: new drug application.

past two years have been the NBEs. Most large companies have proportionately increased R&D spending in the biologics. As part of a recently enacted healthcare reform, US Congress authorized 12 years of data exclusivity for new innovative biologics. In general, the biologics have also experienced higher success rate in drug approval versus small molecule therapies partly due to high target specificity and the ability to modulate targets in unmet medical needs. It is anticipated that by 2015, eight out of top ten pharmaceutical drug products will be the NBEs. The biologics generally serve narrower disease phenotypes and smaller patient size but demonstrate lower side effects because of high target specificity.

The high cost, non-oral delivery, ineffectiveness versus intracellular targets remain as limitations of current biological therapeutics in market.

Generics and supergenerics

The current market share for generic sector is approximately 10% of the global pharma sales but is anticipated to rise to approximately 14% of total pharmaceutical sales by 2015 due to anticipated patent expiry of proprietary products. In the USA, approximately 75% of prescription drugs are believed to be generics and cost approximately 10% of original price. The profit margins in generic market in the USA are getting narrow and

narrower as the manufacturers face intense competition, particularly from India and Israel. This is influencing many pharmaceutical companies (such as GSK, Pfizer, Merck, Abbott) to build strategic partnerships and buyouts in cost-effective regions, particularly India. Many generic drugs are sold as 'branded formulations' or 'established products' in emerging markets (e.g. BRIC countries), where these fetch higher premium approximating 30–80% of original price. The emerging markets are growing but so is the competition and debate on cost containment which is likely to influence profit margins.

The first set of successful biologics that entered market some years back are approaching end of the proprietary protection and will face competition from biosimilars. The long awaited FDA guidelines for approval of biosimilars have been issued recently [Scientific considerations in demonstrating biosimilarity to a reference product: http://www.fda.gov/downloads/Drugs/Guidance-ComplianceRegulatoryInformation/Guidances/UCM291128.pdf]. Unlike small molecule generic market where the competition is deep, the biologics are still viewed as specialty products and the number of competing players is much smaller. The biosimilars and biobetters can claim up to 60–80% of the original product price and remain attractive options for the generic–discovery 'hybrid' model.

Many generic firms are creating innovative collaborations with R&Ds to produce 'supergenerics' or specialty, differentiated products. The supergenerics can be fixed dose combinations, salts, polymorphs, enantiomers, inhalers, dermal patches, new formulations or dosage variations as differentiated alternates to marketed generics. The supergenerics discriminate versus generics in offering improved efficacy, reduced side effects, or niche pediatric doses and can also be potential competition to life cycle management strategies used for proprietary R&D products. With reduced risk and shorter development cycle, the differentiated products have become important strategic component and significant contributor (~45%) to Sandoz' pipeline. Enoxaparin, a generic version of Sanofi's Lovenox, was launched by Sandoz in 2010 and has emerged as the first 'generic blockbuster' product yielding sales of $531 million in first half of 2011 [28] The generic–R&D hybrid is likely to be important constituent of risk balanced portfolio at most large pharma and generic companies.

Drug repositioning, orphan drugs and life extension opportunities

Apart from drug discovery (NMEs and NBEs) opportunities discussed, most large companies are trying to enrich portfolio with low risk options that include life extension for secondary indications, drug repositioning, orphan and neglected diseases or specialty products. Contrary to traditional business model, Genzyme (Sanofi Aventis) flourished targeting only the neglected, rare genetic diseases. The drug repositioning approaches advocated for new uses of existing or clinically discontinued drugs have gained momentum during the past six years. Matching mechanism of the 'off-target' effects of marketed or discontinued drugs with targets or mechanism of unmet indications, several new opportunities are being investigated in clinic. It is believed that
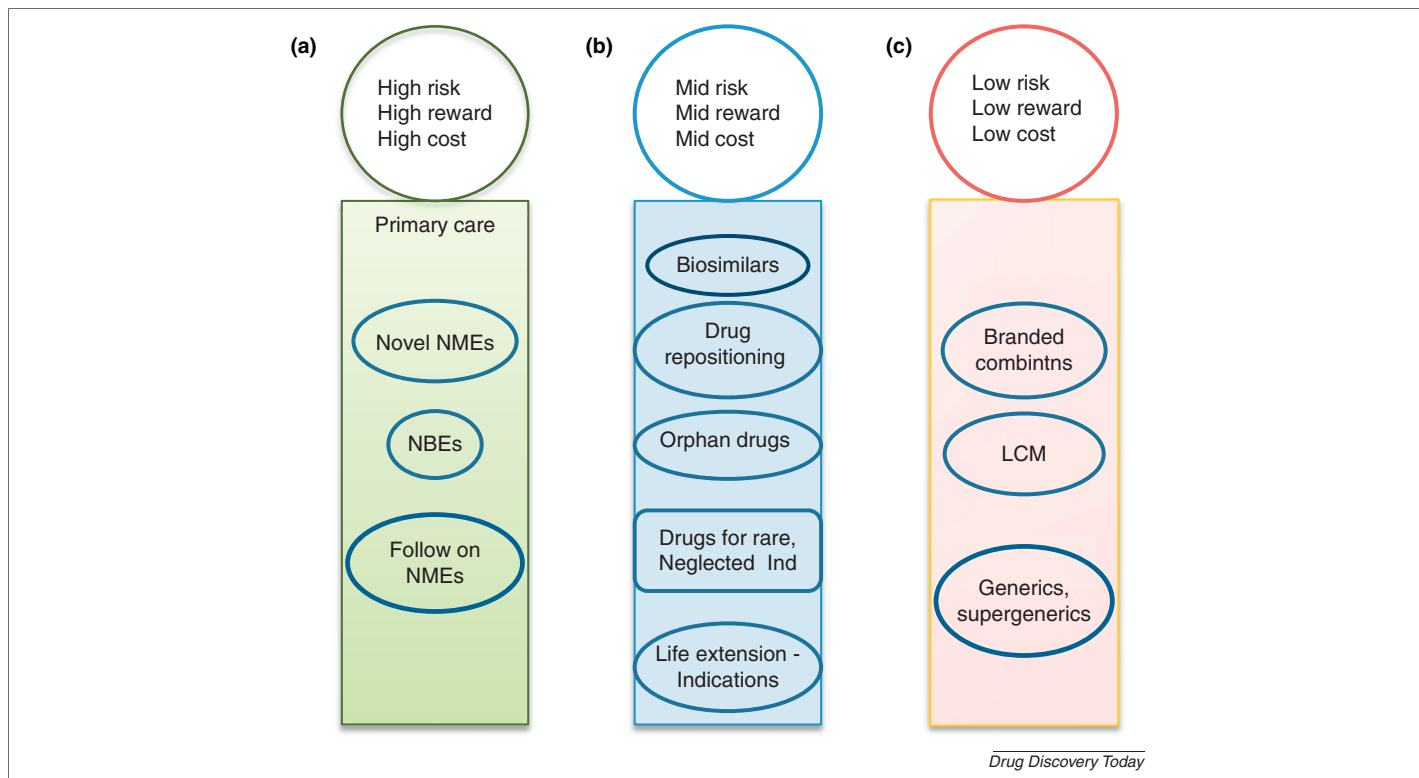

FIGURE 5

Risk balanced portfolio. Tables 1–3 depict assets distribution based on risk–reward ratio. The portfolio of mixed assets from 1, 2 and 3 helps adjust risk.
Abbreviations: LCM: life cycle management; NME: new molecular entities.

there are approximately 23,000 diseases or indications and ≥100,000 marketed or clinically profiled molecules in literature [29]. Screening these molecules versus unmet indications can help identify potential new uses of existing molecules or offer useful starting points for lead optimization. Drug repositioning approaches offer shorter development cycle, reduced development cost and reduced safety, pharmacokinetics profile uncertainty. Several approaches such as phenotypic screening, HTS, molecular modeling either alone or in collaborative mode are being adopted to identify new use for existing or discontinued drugs [30]. More recently, NIH sponsored initiative NCATS (Table 1) is being launched in collaboration with industry partners to seek patented or discontinued drugs from pharma partners for broad screening and identification of molecules with potential utility in rare, orphan or neglected diseases [31]. Guidelines on IP protection and framework for collaboration are being worked out. Several open initiatives, such as CTSA portal, NCGC-NPC browser [32], offer open access to marketed and clinical compounds and encourage industry–academic collaboration to identify treatments for rare diseases. These are relatively early days in drug repositioning approach and only the time will tell if the failure rate in this arena matches failure rates of traditional NMEs.

Most companies are trying to improve productivity and balance risk of their portfolio by working on combination of risk and cost adjusted options shown in Fig. 5.

Non-technical traits

Since the biggest asset for any organization is its 'people power', the research environment and the culture that stimulates creativity and productivity benefits. The mergers and repeated research alignments generally have negative impact on productivity, employee morale and create uncertain surroundings [8]. The vision clarity and organizational stability are important initial steps for getting scientists on board. It is essential that R&Ds create 'innoventive' or innovation driven culture where fear of failure in novel research is eliminated. The discovery leadership has to be inspirational that cultivates high passion, commitment, and love for science. The creative scientists are unconventional thinkers who can feel confined under restrictive environment. The creativity, a fusion of expertise, passion and innovative thinking, can flourish beyond limits in open system. The creative scientists are passionate about research and are driven 'intrinsically' but external environment can have huge impact on the morale and their productivity. The teams that succeed are driven by inspirational, talented scientists that work closely with business leadership. For best results, small teams or units of innovation are important. This is particularly relevant in large companies where individuals can feel identity loss and become disconnected. Transparency and free flow of information is necessary for everyone to stay connected and contribute optimally. Many companies are establishing focused centers of excellence and trying to run each unit as an independent entrepreneur center [http://obrreview.com/2012/newsflash-gsks-discovery-performance [33]]. Some experts also believe that pharma industry should promote 'serendipity exploitation' and 'Black Swan' culture to tap on improbable, unconventional, and out of box research findings [1,34].

Concluding remarks

High failures, high cost, fading pipelines have pushed the pharmaceutical industry into one of its least productive times in history. The industry, however, continues to be enthused by huge opportunities that challenges present. The sector is on threshold of change and is likely to present a different complexion during the next ten years. The players that adopt and respond to challenges will flourish. Emerging models with strong partnerships themes relying on combined wisdom, accessibility to global expertise and specialized skills will evolve. The quality, creativity, speed in deliverables will be critical parameters for success. The industry has history of generating high value and will continue to surpass challenges with innovative scientists and smart utilization of technologies. There is no doubt that the industry will thrive and establish new landmarks.

References

1 Munos, B. (2009) Lessons from 60 years of pharmaceutical innovation. *Nat. Rev. Drug Discov.* 8, 959–968

2 Mullard, A. (2011) 2010 FDA drug approvals. *Nat. Rev. Drug Discov.* 10, 82–85

3 Kunsten, L.J.S. (2011) Drug discovery management, small is beautiful: why a number of companies get it wrong? *Drug Discov. Today* 16, 476–484

4 Thayer, A.M. (2011) Emerging strategies. *Chem. Eng. News* 15–20

5 Vernon, J.A. *et al.* (2010) Drug development costs when financial risk is measured using the Fama-French three-factor model. *Health Econ.* 19, 1002–1005

6 Mullard, A. (2012) 2011 in reflection. *Nat. Rev. Drug Discov.* 11, 6–8

7 FY 2011 Innovative drug approvals. *US Food and Drug Administration Report*, 2011, 1–29

8 LaMattina, J.L. (2011) The impact of mergers on pharmaceutical R&D. *Nat. Rev. Drug Discov.* 10, 559–560

9 Kola, L. and Landis, J. (2004) Can the pharmaceutical industry reduce attrition rates? *Nat. Rev. Drug Discov.* 3, 711–715

10 Graul, A. *et al.* (2009) Overcoming the obstacles in the pharma/biotech industry: 2008 update. *Drug News Perspect.* 22, 39–51

11 Graul, A. *et al.* (2010) Overcoming the obstacles in the pharma/biotech industry: 2009 update. *Drug News Perspect.* 23, 48–63

12 Graul, A. *et al.* (2011) The year's new drugs & biologics, 2010. *Drugs Today (Barc.)* 47, 27–51

13 Arrowsmith, J. (2011) Phase II failures: 2008–2010. *Nat. Rev. Drug Discov.* 10, 328

14 Arrowsmith, J. (2011) Phase III and submission failures: 2007–2010. *Nat. Rev. Drug Discov.* 10, 87

15 Swinney, D.C. and Anthony, J. (2011) How were medicines discovered? *Nat. Rev. Drug Discov.* 10, 507–519

16 Paul, S.M. *et al.* (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nat. Rev. Drug Discov.* 9, 203–214

17 Andersen, M.R. *et al.* (2011) Trends in the exploitation of novel drug targets. *Nat. Rev. Drug Discov.* 10, 579–590

18 Andersson, S. *et al.* (2009) Making medicinal chemistry more effective – application of lean sigma to improve processes, speed and quality. *Drug Discov. Today* 14, 598–604

19 Meanwell, N.A. (2012) Synopsis of some recent tactical application of bioisosteres. *J. Med. Chem.* 54, 2529–2591

20 Gleeson, M.P. (2008) Generation of a set of simple, interpretable ADMET rules of thumb. *J. Med. Chem.* 51, 817–834

21 Bonabeau, E.N. *et al.* (2008) A more rational approach to new product development. *Harvard Bus. Rev.* 86, 96–102

22 Kneller, R. (2010) The importance of new companies for drug discovery: origins of a decade of new drugs. *Nat. Rev. Drug Discov.* 9, 867–882

23 Fieldman, M. *et al.* (2003) TNF defined as a therapeutic target for rheumatoid arthritis and other autoimmune diseases. *Nat. Med.* 9, 1245–1250

24 Goldman, M. (2011) Reflections on the innovative medicines initiative. *Nat. Rev. Drug Discov.* 10, 321–322

25 Talega, P. (2009) Open innovation share or die. *Drug Discov. Today* 14, 2003–2005

26 Tralau-Stewart, C.J. *et al.* (2009) Drug-discovery: new models for industry–academic partnerships. *Drug Discov. Today* 14, 95–101

27 Mullard, A. (2011) Partnering between pharma peers on the rise. *Nat. Rev. Drug Discov.* 10, 561–562

28 Thayer, A.M. (2011) Shifting generics to the super side. *Chem. Eng. News* 22–26

29 Persidis, A. (2011) Systematic repositioning using MoA to map all drugs against all diseases. *The Drug Repositioning Conference*, San Francisco, July 13–14

30 Doan, T.L. *et al.* (2011) The future of drug repositioning: old drugs, new opportunities. *Annu. Rep. Med. Chem.* 46, 385–401

31 Mullard, A. (2011) Could pharma open its drug freezers. *Nat. Rev. Drug Discov.* 10, 399–400

32 Huang, R. *et al.* (2011) The NCGC pharmaceutical collection: a comprehensive resource of clinically approved drugs enabling repurposing and chemical genomics. *Sci. Transl. Med.* 3, 80ps16

33 Douglas, F.L. *et al.* (2010) The case for entrepreneurship in R&D in the pharmaceutical industry. *Nat. Rev. Drug Discov.* 9, 683–689

34 Taleb, N. (2007) *The Black Swan: The Impact of the Highly Improbable*. Random House