Why and how have drug discovery strategies in pharma changed? What are the new mindsets?

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Teaser: The key points emerging from the different R&D approaches and enabling all scientists working in the drug discovery domain to develop innovative medicines for the 21st century are provided in this original review.

Keywords: Open innovation; generics; biosimilar; pheontypic and target based discovery; best-in-class; first-in-class; personalized medicine; companion diagnostics.

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Author biographies

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Serge Mignani joined the Catholic University of Louvain-la-Neuve (Belgium) for a PhD training under the supervision of Professor H.G. Viehe. Then, he joined the University of Madison (USA) for a postdoctoral stay under the supervision of Professor B.M. Trost. In 1981 he joined Rhône-Poulenc (currently Sanofi) at the Vitry Research Center, where he was Head of the Medicinal Chemistry Department and Scientific Director. More than ten clinical candidates have been disclosed by his team. Serge Mignani is author of more than 120 publications and over 100 patents. More than 70 invited plenary lectures and conferences have been presented. Serge Mignani was nominated (2014) as Professor at the Euro-Mediterranean University of Fez, Morocco.

João Rodrigues

João Rodrigues received his PhD (1999) in chemistry/inorganic chemistry from the University of Lisbon (Portugal). He is a staff member of the University of Madeira (Madeira Island, Portugal) and responsible for the areas of inorganic and organometallic chemistry, nanochemistry and nanomaterials. Since 2013, he has belonged to the General Council of the University of Madeira. Since 2006, he has been the head of Centro de Química da Madeira (National Research Unit) and since 2012 he has been the director of the Master in Nanochemistry and Nanomaterials. Presently, he belongs to the board responsible for the roadmap for health and wellness in the framework of 'Horizon 2020' (Madeira 14-20) at Madeira Island (Portugal). He was a visiting scientist in several universities abroad (namely in China, India and Brazil) and serves as a referee for several peer-reviewed journals. His students (Post-docs, PhDs and Masters)

have obtained positions in several universities and companies in Portugal and abroad (e.g. USA, Sweden, Brazil and China). His main research interests are based on the design, synthesis and characterization of dendrimers/metallodendrimers, molecular wires, nanoparticles and polymers for optoelectronic and biomedical applications (e.g. emerging and infectious diseases and oncology).

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Jean-Pierre Majoral is Emeritus Director of Research at the CNRS in Toulouse. His research interest is focused on the design and the properties of macromolecules such as phosphorus dendrimers and hyperbranched polymers, with key efforts directed to the use of dendrimers in medicinal chemistry and material sciences. Emphasis is also on immobilization of molecular and macromolecular organo- and metalo-catalysts and their use for fine chemical synthesis. He has received numerous prestigious awards from Germany, Poland, Spain, UK and France. He is a member of several Academies of Sciences worldwide and an author of 590 publications and 45 patents.

In the pharmaceutical industry the long-term challenge of drug innovation is the key phrase throughout R&D that refers to increasing the output of original drug candidate molecules. To increase R&D productivity, implementation of new and strategic R&D orientations to develop new approaches or systems to identify hits and leads efficiently has taken place and enabled all scientists working in the drug discovery domain to develop innovative medicines for the 21st century.

Introduction

The pharmaceutical industry is currently facing huge challenges to overcome strongly growing economic pressure. Pharmaceutical companies must find new approaches to improve productivity and increase their output of original drugs, not only to satisfy demands of the healthcare sector to increase the life expectancy and quality of life of billions of people but also to ensure their business survival in terms of return on R&D investment [1,2]. Today, R&D organizations must strive to achieve drug innovation to address important issues such as the strong decrease in the number of new chemical entities launched every year and the eroding patent estate. Their main objective is to deliver hits, leads and finally drug candidates of the highest possible quality to decrease the risk of failure in clinical phases at the end of the development process.

Herein, we highlight and analyze the key points emerging from the different R&D approaches that have been implemented and that have offered scientists working in the drug discovery domain insight into the invention and development of innovative medicines of the 21st century. The question posed by everybody involved in drug discovery is which of these key points represent the best strategy to create and to develop new drugs? The aim of this work is to provide the readers with a broad vision for new hit, lead and drug optimization processes using the space concept strategy and metrics.

The pharmaceutical industry's grand challenge

Economic impact of the pharmaceutical industry

The economic impact of biopharmaceuticals can be simply evaluated by the number of direct jobs, which is more than 810 000, and of total jobs (including indirect and induced jobs), which is nearly 3.4 million, created by the sector [3]. The market could be worth nearly US\$1.6 trillion by 2020, up from US\$1.1 trillion in 2011 [4]. The R&D-based pharmaceutical industry spends over US\$100 billion per year [5]. Clinical trials account for 63% of this, whereas the cost of preclinical drug discovery and development is estimated to be only 32% [6]. In 2011, 5408 medicines were in clinical development worldwide, with around 2000 each in Phase I and Phase II, and approximately 850 were in Phase III. Many of the medicines in clinical development are for more than one medical application [3].

Pharmaceutical industry under pressure

Over 400 new medicines received approval between 2000 and 2012 [3]. In 2013, although more than 5000 medicines were in development globally, only 25 innovative new medicines [known as new molecular entities (NMEs)] and two biologics were approved by the FDA, accounting for 31% of the decline in approvals from 2012 [7]. Interestingly, many of the 2013 approvals offer exceptional earning potential. Indeed, 48% of the new approved medicines are set to achieve over US\$1 billion in annual sales within 5 years [7]. There is renewed hope because much of the pharmaceutical industry began to show signs of recovery in the second half of 2013 sales and earnings. Nevertheless, from a global point of view, the sales and earnings in 2013 of big pharmaceutical companies continued to decline, down by 1% and 3.2%, respectively; whereas those of biotech companies rose by 12.6% and 12.9%, respectively [8], and returns on R&D investments continue to fall [9].

Importantly, 2014 was a good year for pharmaceutical productivity with 31 NME and 11 biologic license applications, representing the best record since 1996. The FDA-approved drugs include eight cancer drugs (18%) and 12 drugs that are broadly distributed against infectious diseases (27%), four of which are antibiotics. Seventeen approved drugs showed novel mechanisms-of-action. About 65% of drugs were in-licensed or acquired and about 40% of the 2014 FDA-approved drugs target rare diseases (five approved drugs, 11%). The aggregated sales were US\$53 billion and US\$48 billion in 2013 and 2014, respectively [10]. In short, their business relies on a costly, risky and time-consuming hunt for novelty in drug candidates (first-in-class medicines to treat diseases with as-yet no treatment), genes and targets. New drugs must be more efficacious than those currently on offer,

and should permit, for instance, shorter hospital stays to justify a higher cost to third-party payers. In spite of the forced reduction in R&D productivity and the eroding revenues from established drugs owing to strong generic competition (small organic molecules) and in the near future to biosimilar competition [i.e. the antibody (Ab) field], the pharmaceutical industry needs to produce sustainable revenues and returns on investment for shareholders, which partly explains its addiction to blockbuster drugs. Concerning the small organic molecules, the generic share of prescriptions rose from 54% in 2003 to 84% in 2012, and will rise about 87% by 2017 [12]. In 2013, 16 biosimilar products were under development [13]. The first biosimilar monoclonal antibody (mAb) approved by European Medicines Agency (EMA) regulators was Inflectra™ which is a copy of Johnson & Johnson's infliximab used to treat several inflammatory diseases (e.g. psoriasis, rheumatoid arthritis, etc.) [14]. After several years of debate, the FDA has approved Sandoz's Zarxio™. Zarxio™ is the first biosimilar drug available in the USA, is a copycat version of Novartis's Neupogen® and is a granulocyte colony-stimulating factor (G-CSF) analog used to stimulate the proliferation and differentiation of granulocytes [15].

Scientific and strategic challenges for pharmaceutical industries: an overview

Over the past decade, the drug industry has faced two major challenges, one scientific and one strategic. The scientific challenge concerns the translation from genomic information gathered to understand disease predisposition and progression as well as to predict a patient's response to drugs [16]. Thus, over the past several years, a strong emphasis has been given to the development of genomic and bioinformatics approaches to identify new biomarkers [17] or candidate drug targets [18]. This genomics and proteomics revolution has produced thousands of new targets for drug discovery [19]. Biomarkers can be considered as parameters or indicators that can be used to measure and evaluate: (i) normal biological processes; and (ii) the effects on biological systems of several agents such as drugs, as well as biological or physical agents. For instance, in oncology the main biomarkers are proteins [e.g. prostate-specific antigen (PSA), human epidermal growth factor (HER2), CK7], circulating tumor cells (e.g. p53), mRNA, radiological analysis [e.g. positron emission tomography (PET) scanning, molecular resonance imaging (MRI)], among others [20]. The use of biomarkers in Phase I/II trials to select patients can accelerate anticancer drug development [21].

Based on the analysis of 113 first-in-class drugs, between 1999 and 2013 the majority had been discovered using a target-based approach (~71%: 41% small molecules; 30% biologics) versus systems-based approaches (~30%: 23% chemocentric; 7% phenotypic screening). First-in-class drugs can be classified as follows: systems-based compounds comprising small molecules (~50%) and natural products or substances (~37%); or target-based compounds comprising biologics (~42%), small molecules (~38%) and natural products or substances (~20%). The major drug-targeted families, G- protein-coupled receptors (GPCRs), kinases, proteases and ion channels are absent or under-represented among drugs discovered via systems-based approaches [22]. Currently, the main different approaches to obtain chemical leads that are fully integrated in the early drug discovery processes are from natural products, from HTS, from existing drugs and from fragment-based discovery (FBDD) [23].

Generally speaking, drugs can fail in clinical trials or have delayed market entry as a result of the display of detrimental or fatal side-effects, which can be considered as a balance between different biological systems. The challenge is to analyze the side-effects globally and not only at the cellular, organ and human patient levels. For decades, the pharmaceutical industry has been actively working to drive down the important cost of drug failure in terms of time and money. Indeed, implementing strategies to identify the failures as early on in the process as possible is absolutely crucial, because failures during early stages are less costly than those at Phase III. Despite best efforts, failures in clinical trials have soared over the past 20 years, with attrition rates between 1990 and 2010 increasing for Phase I from 33% to 46%, for Phase II from 43% to 66% and for Phase III from 20% to 30%. The current reasons for failure at Phase II are insufficient efficacy (51%), safety concerns

(19%), strategic issues (29%) and pharmacokinetics/bioavailability issues (1%); and reasons for Phase III failures are insufficient efficacy (66%), safety concerns (21%), financial or commercial concerns (7%) as well as non-disclosed issues (6%). Generally speaking, new drug success rates in Phase II are about 20% (51% insufficient efficacy and 19% safety concern) and about 50% in Phase III (66% insufficient efficacy and 21% safety concerns) [24]. During R&D, success at each step is mandatory, but 'good' earliest strategic choice remains crucial. Figure 1 highlights the main reasons for clinical failures by Phase for 410 drugs that entered human testing between 2000 and 2009 [25]. The main failures in Phase II and III studies are efficacy issues, 54% and 52%, respectively. Safety issues represent about one-third of all the 410 drugs analyzed in Phase I and Phase III studies, versus 17% of all Phase II studies.

New strategic vision in drug discovery

General aspects

The development of a new and sustainable funding model with public and academic participations has become an urgent requirement [26]. To address this, new hubs are emerging that group together different research systems including academia, research institutes, the American National Institutes of Health (NIH) and the pharmaceutical industry, including biotechnology companies. Their aim is to put an end to these different sectors, each with their own drug-finding processes and objectives, working alone in their respective corners. Indeed, until recently, the motto 'every man for himself' has led to a lack of shared capitalization on collective scientific and technological knowledge and knowhow [27]. Much enthusiasm now surrounds an emerging translational research concept referring to the novel integration of discoveries into a common framework that could change the landscape of drug discovery [28]. Although still in its infancy, a recent article by Fishburn analyzed the roles taken by the different 'actors' and their respective contributions and benefits to the collective organization with the common goal of increasing the number of drugs successfully brought to market [29]. This study found that the most important investments are currently made by pharmaceutical companies and the NIH.

Doing the right things or doing things right

In this direction, Elebring [30] recently published a very instructive article that addressed the crucial question distinguishing the most important approach in current drug discovery: are we doing the right things or doing things right? The author found that the key points to consider in the drug discovery process are the right pharmacologic target and the right chemical lead. The major conclusion was that the quality of R&D and drugs can reduce timelines and costs. We fully agree that the right selection of these two key elements ensure an improved R&D productivity and the implementation of robust pipelines, whatever the strategy used: target-based screening or phenotypic screening approaches. Based on this principle, in Figure 2 we propose – like a 'mantra' for R&D – a discipline for pharmaceutical R&D aimed at improving productivity and efficiency in the generation of new drugs as a marriage between quality, speed and cost – developed by Elebring [30] – and druggability and quality of the clinical candidate, druggability and quality of the target and, the final objective, clinical efficacy of the drug. We fully agree with the comments of Elebring: 'Focus on science quality should lead to improved drug discovery quality, cost and speed' [30]. The high-quality of the bioactive molecule can be evaluated using several criteria such as e-ADME profile including PK/PD behaviors, metrics, drug-like concept [31], among others; whereas the target must be validated using several techniques [32]. The improvement of the quality of the target and bioactive molecule decrease the probability of failure in clinical trials. Reduction of time and cost (R&D) are strongly related to the high-quality of science. Recently, Kinch highlighted target selection for FDA-approved medicines [33].

Open innovation as a model to find and to develop new drugs

Twenty years ago, drug discovery was exclusively conducted within pharmaceutical organizations. Today, in the open innovation model, pharmaceutical companies commercialize not only their own ideas but also a considerable proportion of inventions and innovations from external organizations. One of the major challenges of the open innovation era is ensuring its strong integration within each of the different partners and a high level of coordination [34]. By encouraging a dynamic innovative environment with strong collaborations among pharmaceutical industries, academia and other industries, the open innovation mindset is a key to developing sources of solutions. Four new types of open innovation, 'knowledge creation', 'knowledge integration', 'knowledge translation' and 'knowledge leverage' have been described by Schuhmacher *et al.* [27]. The development of nanopharmaceuticals under open innovation is a good example of this new approach and has been analyzed by Eaton [35].

Strategic mergers and acquisitions in the pharmaceutical and biotech industries

The losses of the major revenue as a result of patent expirations have forced big pharmaceutical companies to scale patent cliffs and to look to biotech companies and others to: (i) fill in their pipeline; (ii) create consolidation purpose; (iii) achieve R&D cost reduction; (iv) produce synergies; and (v) create a breakthrough innovation, but with important social consequences (i.e. job cuts, psychological disorders, etc.) [36]. Thus, for instance, Merck will cut 8500 jobs by the end of 2015 saving US\$2.5 billion [37]. The recent expiration of the blockbuster drug patents are as follows: Plavix® (clopidogrel), Lipitor® (atorvastatin calcium) and Seroquel® (quetiapine fumarate), inducing massive drops in revenue of US\$33 billion [38].

Today, half of all drugs are developed through collaborations, one-quarter of which are part of a merger, acquisition or co-development arrangement. In addition, 49% of pharma drug development arrangements are licensing, 25% co-development, 24% merger and acquisition and 2% joint ventures [39]. An analysis performed by Elvidge showed the decline of the megadeals and the development of late-stage deals. More than 60% of the deals have been performed by big pharmaceutical companies [40]. For an interesting example, three leading pharmaceutical firms (Novartis, GSK and Eli Lilly) are set to exchange business segments in deals affecting at least 14 000 employees, to reinforce their strongest businesses, Novartis in oncology, GSK in vaccines and Eli Lilly in animal health, and exit weaker ones [41]. In addition a joint venture has been set-up between GSK and Novartis focusing on cancer immunotherapy, epigenetics and tumor microenvironment [42]. Based on the interesting analysis of Kinch *et al.* [43], the evolution of major organizations – mainly business entities – controlling NMEs has been highlighted in Figure 3. From 1930 to 1960 the steady increase of the number of approved NMEs correlated with the proportional expansion of the organizations. From 1960 to 1980 the number of NMEs increased whereas the number of organizations that had obtained NMEs reached a plateau, with few new entries or exits. Starting in the 1980s, prominent change in drug discovery and development was observed. New companies such as start-up companies and biotechnology companies have seen the day and, at the same time, exits were largely caused by consolidation strategies (mergers and acquisitions) rather than bankruptcies.

Strategic generics and biosimilars in the pharmaceutical industry

Generic copies are pharmaceutically equivalent to the originator medicine, and represent a new vision in the pharmaceutical industry [12]. The market boom for generics as a result of the patent expiration (off-patent – the so-called patent cliff) has led to an abrupt drop in sales of medicines such as blockbusters. In the USA, they represented 19% and 86% in 1984 and 2013, respectively, and represent the pillar of healthcare, with ~US\$1.5 billion of savings. Interestingly, in 1990, 50% of the new drug applications were from the USA and 15% were from India, whereas today 30% are from the USA and 40% are from India. Figure 4 represents the main suppliers of generic drugs and the 2013 generic drug sales. According to Frost & Sullivan's report, between 2010 and 2017

pharmaceutical products worth US\$150 billion will go off-patent. The generic drugs market revenues will grow from ~US\$124 billion (2010) to ~US\$231 billion (2017) with strong generic drug manufacturer competitions. The manufacturers Teva, Sandoz and Mylan decided to produce higher value generics. Another strategy adopted by generic drug manufacturers is to set-up alliances with branded pharma for marketing and exclusivity rights to generic blockbusters such as Lipitor® and Crestor®.

Biosimilars are revolutionizing the bioprocessing industry as functional replicas (antibody copy) of the originator biologic drugs [44]. The biosimilar market shows significant growth, mainly because of the launch in the next few years of numerous mAb biosimilars of mAbs where the patent will expire such as trastuzumab (Herceptin® from Roche) and adalimumab (Humira® from Abbott). Already, the European regulators have approved in 2013 the first biosimilar mAb, Inflectra™ (Hospira), which is the biosimilar of Johnson & Johnson's Remicade® (infliximab) to treat several inflammatory diseases such as psoriasis and rheumatoid arthritis. In 2012, the sales of Remicade® were more than US\$8 billion worldwide. Today, nine biosimilars of Remicade® are under development, 16 for Humira® (adalimumab; inflammatory diseases), 21 for Enbrel® (etanercept; inflammatory diseases), 34 for Rituxan® (rituximab; cancers and arthritis), 30 for Herceptin® (trastuzumab; cancers) and 16 for Avastin® (bevacizumab; cancers). The global biosimilars market revenue was estimated at around US\$172 million in 2010, and should be more than US\$4 billion in 2017, with an annual growth rate of about 56%. The European Union (via the EMA), is the first region to adopt legislation allowing the registration of biosimilars based on biosimilar guidelines related to similarity to the reference product. Very recently, the FDA approved Sandoz's Zarxio™ and, interestingly, generics of nanodevices in medicine [45].

Strategic visions to find and develop medicines

Has the modulation of a network of targets outdated the one-disease–one-target philosophy as the best strategy to find new drugs?

A new paradigm is emerging in pharmacological research called polypharmacology, which describes the activity of compounds at multiple targets. The multifaceted goal is to avoid adverse side-effects (safety parameters), and to improve therapeutic efficacy, prevent drug resistance or reduce therapeutic-target-related adverse side-effects (efficacy parameters). As indicated by Peters, since the 1990s the pharmaceutical industry has focused its attention on searching for highly selective drugs – at the early stages of drug discovery – to avoid adverse side-effects [46]. Lack of selectivity was until then usually discovered later on in a drug discovery project. Generally, multitarget drugs – in combination or not – are more efficacious than single-target drugs, for instance in oncology and against viral infection. Furthermore, rather than a one-target therapy, polypharmacological modulation of a network of targets is actually required in the treatment of many multigenic diseases. For instance, multikinase inhibitors can block multiple targets in parallel signaling pathways and thereby prevent drug resistance caused by mutations or expression changes [47].

First-in-class versus best-in-class and phenotypic- versus target-based drug discovery: what matters for commercial success?

The development of genomics and proteomics has produced a plethora of targets for drug discovery. The main challenges are the validation of these new targets in specific human disease [48], and then the efficacy of the corresponding treatment in humans. The pharmaceutical industry is facing a challenge of productivity in R&D. Thus, innovation strategy in discovery represents the most powerful strategy to find new drugs [49]; for instance, based on the discovery of new targets to deliver more and better drugs in the pipeline. Ideally, the pharmaceutical industry focused on first-in-class products (hypothesis-driven) based on new targets, but this strategy alone is not enough to

solve the current productivity gap. The scientific knowledge is fundamental to the discovery of ‘first-in-class’ medicines that are based on many different biochemical mechanisms mediating the drug response at the target [22]. In addition, projects based on new targets have less probability to reach the market than those based on known targets, and the later entrants – where research is based on known targets – displace the first-in-class products in the market place, even if the first entrant has the exclusivity free of competition during a period of time [50].

Generally speaking, the semi-empirical phenotypic-based discovery does not require understanding of the mechanism-of-action but the understanding of the biology related to the disease with the risk to develop compounds without any understanding of the mechanism-of-action to evaluate dose–response relationship. A target-based discovery approach is based on a clear understanding of the mechanism-of-action allowing the selection of the biomarkers for patient stratification, development of target therapy and combinations.

Innovation requires high investment in R&D and is time consuming. The late entrant (rival) developing a best-in-class strategy achieved major commercial success, such as the blockbusters atorvastatin calcium (Lipitor®) from Pfizer and lovastatin (Mevacor®) from Merck. Pharmaceutical companies producing such first-in-class drug candidates often develop a ‘follow-on’ drug based on the more validated (with the first drug) target to reduce the risk of obtaining no drug approval. Figure 5 represents the evolution of the FDA-approved first-in-class and follower drugs between 1999 and 2013 analyzed by Swinney and Anthony and Eder *et al.*

In an early study, Swinney and Anthony emphasized that, between 1999 and 2008, based on the number of NMEs, phenotypic screening was the most successful strategy to find first-in-class drugs whereas target-based screening was the most efficient at finding follow-on drugs [51]. The mechanism-of-action used by the majority of small-molecule first-in-class NMEs involved enzyme inhibition or receptor modulation. An important conclusion is that phenotypic screening enabled the discovery of biologically active compounds (drug leads and clinical candidates) that are more likely to have relevant mechanisms-of-action.

Another analysis by Eder *et al.* [22] on all the 113 FDA-approved first-in-class drugs between 1999 and 2013, shows that the majority had been discovered using a target-based approach (~71%: ~41% small molecules; ~30% biologics) versus systems-based approaches (~29%: ~22% chemocentric; ~7% phenotypic screening). First-in-class drugs can be classified as follows: systems-based compounds comprising small molecules (~50%) and natural products or substances (~37%); or target-based compounds comprising biologics (~42%), small molecules (~38%) and natural products or substances (~20%). Chemocentric approaches represent the identification of active compounds from, for instance, plants and derivatives, microbial extracts, serendipitous findings, among others. Numerous examples of drugs already identified using the chemocentric approach can be highlighted such as aspirin, nitisinone, nelarabine and ezogabine. In addition, the authors highlighted that phenotypic screening represents not only an important source of new drugs but also the development of new biology and pharmacological tools.

Today, about 70% of drugs within the pipeline are potential first-in-class medicines, the proportion of which varies according to therapeutic field: neurology (84%), cancer (80%), psychiatry (79%) and immunology (72%) [52]. The major drug-targeted families, GPCRs, kinases, proteases and ion channels are absent or under-represented among drugs discovered via systems-based approaches. Currently, the main different approaches to obtain chemical leads that are fully integrated in the early drug discovery processes are: from natural products, from HTS, from existing drugs and FBDD. Another interesting analysis has been performed by Schulze and Ringel showing that it is the same to be first-in-class with a best therapeutic advantage or to be best-in-class – also with a best therapeutic advantage – but second within no more than 2 years after the launch of the first drug [53]. Moffat *et al.* highlighted that, in the oncology domain, the target-based discovery approaches remain the main strategy used, but phenotypic screening also contributed to cancer drug discovery, for example cytotoxics are drugs against mitotic arrest [54].

Recently, Zheng *et al.* presented an interesting review about the renewal of phenotypic screening,

as a new momentum in drug discovery. The new applications of phenotypic screening of known drugs are: (i) to identify new indications especially for diseases without effective therapies; and (ii) to repurpose new screens for new target identification purposes [55]. Table 1 summarizes the average costs and the length of time it takes for a drug to be FDA-approved related to drug discovery strategies.

Figure 6 shows the crossroad between phenotypic (empirical) and target (molecular) based discovery strategies for best-in-class and first-in-class medicine discovery. All options are theoretically possible. Importantly, as postulated by Swinney [51], the unmet medical need should be tackled via the following chronological pathway: (i) phenotypic assay related to the unmet specific human disease affording first-in-class active derivatives; (ii) target identification process to link the specific mechanism-of-action and the phenotypic screening; and (iii) target-based discovery approach to find best-in-class drugs. This progression is correlated with the iterative increase in knowledge from empirical analysis (early stage) to strong knowledge of the specific molecular mechanism-of-action. In Figure 7 we present an overview of the main strategies developed to find and to produce new small-molecule drugs. These strategies are based on the knowledge or not of the target such as protein structure and the structure of the ligand related to this target. It is not in the scope of this review to present and to analyze the different strategies developed to find new medicines [56], but only to represent an overview.

The future of pharmaceutical science related to industry and academia

Interestingly, Crommelin *et al.* proposed four potential scenarios for the pharmaceutical sciences in 2020 based on the identification of four potential scenarios [57]. As shown in Figure 8, the matrix can be divided in four parts: (i) scenario 1 (pharmaceutical companies: innovation spirit; academia: public-private partnerships); (ii) scenario 2 (pharmaceutical companies: new types of businesses based on lifestyle technologies; academia: spins-off companies, public-private partnerships); (iii) scenario 3 (pharmaceutical companies: niche markets; academia: source of fundamental knowledge, few public-private partnerships); and (iv) scenario 4 (pharmaceutical industries: only clinical trial development corresponding to the decline of majors; academia: drug-finding strategy, few public-private partnerships). These four scenarios are at the crossroads of two aspects of the science: scientific culture (knowledge to develop and market new drugs) and treatment and prevention of the diseases (societal attitudes). In Figure 8 only the pharmaceutical and academic views are presented.

An at-a-glance vision for new hit, lead and drug optimization processes using the space concept strategy

The nearly infinite number of potential drugs present in the chemical space continuum of biological systems encompasses all possible organic molecules and is limited only by the chemist's imagination. The main challenge left to face in the discovery and development of new medicines is scouting the richly diverse chemical space in the search regions that contain specific biologically active derivatives with adequate physicochemical or topological properties. Since the introduction by Lipinski and Hopkins of the concept of navigation and exploration inside the less-well-trodden chemical spaces in biology and medicine, many efforts have been made to find and to develop original drugs [58]. The objective of medicinal chemistry is thus to expand the druggable chemical space by the identification of new regions, thereby paving the way to finding new drugs, in particular those required for challenging targets [59]. The concept of drug-like chemical space has widely been used in drug development for the selection of molecules to be screened, tested or selected, as well as for the assessment of the quality of the hit and lead compounds or final drugs. A far-ranging goal of this research is to identify new discrete chemical regions (called clusters, subtractions, etc.) to find and to develop original drugs, especially for challenging targets.

Inspired by the Lipinski and Hopkins concept of navigation and exploration of the chemical space,

we propose in Figure 9 a simple overview for new hit, lead and drug optimization process using the space concept strategy and several metrics to qualify these different chemical entities. For instance, the virtual and real chemical space can be subdivided into four subareas (also known as clusters) associated with several specific characteristics. Thus, these four subset chemical regions have been parameterized using a large number of specific chemical and physicochemical properties or topological descriptors as recognition patterns. For example, a region might be described based upon its eADMET properties, drug-likeness *in silico* or Lipinski's rule-of-five (Ro5), indicating the possible oral bioavailability of drugs via passive absorption from the intestine. Importantly, Ro5 also determines the boundaries of spaces for appropriate potential druggable final drugs.

As shown in Figure 9, four clusters have been parameterized, for instance by MW, clogP, number of hydrogen acceptors (NHA) and number of hydrogen donors (NHD), to define discrete areas such as the drug-like chemical space (Lipinski's rule-of-five, Ro5, oral route, grey cube), lead-like chemical space (Oprea's criteria, rule-of-four, Ro4, green cube), fragment chemical space (rule-of-three, Ro3, bright blue cube) and one mauve cube dedicated to the Ro5² for transdermal drugs. Other spaces dedicated to other administration routes can be used (mauve cube) [60].

Inside the Ro5 (clinical candidates), Ro5' (clinical candidates) and Ro4 (leads), first we recommend LE as a simple indices or metric to quantify the molecular quality of the different chemical entity types, for selection and optimization inside each cluster. Other indices can be used such as LLE, BEI/SEI, SIHE or QED. QED is used only for clinical candidates. The optimization navigation process between each cluster can be performed using LE (Figure 9), LLE or BEI/SEI [61]. Based on these metrics, construction of more druggable libraries (from fragments, leads or drugs) can be developed.

The overlapping of the drug-likeness chemical space continuum (Ro5, grey cube) and the 3D target classes (block-cylinder, also called target space) including individually, for instance, PPI space, kinase space, GPCR space, defined an overlap volume (green rays, truncated cylinder) for which all the compounds (virtual or real) within this space are druggable; the anti-overlap area corresponds to the poorly druggable compounds.

The same parameters used to define the boundaries of druggable compounds (e.g. Ro5) can be used to define a specific target space including drugs.

Concluding remarks and future perspectives

With our combined expertise gained in the pharmaceutical industry and academia, in this concise review, we present our common analysis on why and how drug discovery strategies in pharmaceutical companies changed. Drug discovery represents the first step in the creation of new drugs, and occurs in academic institutions, biotech companies and large-medium pharmaceutical companies. Throughout the past one-to-two decades, the decline in R&D productivity, in other words the decrease in output of truly new drugs, has led to a pharmaceutical crisis. Multifaceted strategies have been implicated to overcome the pressure such as: (i) increased expenditure on R&D; (ii) enhanced mergers, deals and acquisitions; (iii) reinforced product in-licensing capabilities; (iv) implementation and reorganization of new R&D facilities to cater for new and powerful technologies such as computational chemistry, focused HTS, fragment approaches and genomics, proteomics or metabolomics approaches, among others; (v) development and implementation of tools that help remove part of the uncertainty element of pharmaceutical research, such as druggability prediction methods favoring production of high-quality active compounds, and new metrics of ligand efficiency; (vi) development of new pharmaceuticals to open up new markets, for example orphan drugs, personalized medicine; (vii) development of an open innovation strategy; and (viii) considerable staff cutbacks.

In this review we have analyzed the main new strategies in drug discovery aimed to disrupt the spiral of decline in R&D productivity. We believe that the first step R&D should be taking is to develop strategies to deliver high-quality clinical candidates based on druggable building blocks, fragments, hits and leads, for instance using fragment-based approaches. The second step to take

would then be to develop druggable targets either from patients, using a biomarker strategy, or from validated targets to decrease the clinical attrition rate. Another direction is the development of personalized medicine associated with companion diagnostic tests not only in the domain of oncology but also in other therapeutic fields. We fully agree with the important point made by Elebring [30] that ‘too much process thinking in drug discovery, such as Ro5, Ro3 etc., can block enthusiasm, creativity, intuition, innovation and serendipity’. Future success in drug discovery must therefore depend on achieving the correct balance between ‘doing the right things and doing the things right’. Recently, Bennani [62] introduced a new concept, termed ‘innovation ASAP’, the expansion of which we believe would further enhance innovation culture – already a hot topic in many other industries – inside the pharmaceutical industry. The embracing of such a concept is required to stimulate the delivery of more and improved next-generation drugs through the pipeline for currently untreated diseases, and to shape the pharmaceutical R&D business toward effective prosperity. The rethinking by the pharmaceutical industry of major innovation strategies, such as the implementation of the ‘open innovation/disruptive innovation’ principle across the entire R&D process, represents one of the main goals toward achieving success.

Getting the right balance between first-in-class products based on new targets and second-in-class products, as well between target-based and phenotypic approaches, constitutes a lifeline offering the chance to resolve the drug pipeline attrition. In addition, to reduce risk of failure in early clinical trials and reduce production costs, pharmaceutical companies should invest more time in the development of the phenotypic screening approach as a repurposing screen of already approved drugs to identify: (i) new indications for diseases without an effective therapy; and (ii) new targets (rare or neglected diseases). The take home message should be that progress in drug discovery can be achieved with the association of three mindsets: information, education and collaboration.

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Figure legends

Figure 1. Main reasons for clinical failures by Phase based on 410 drugs that entered human testing between 2000 and 2009. The main failures in Phase II and III studies are efficacy issues, 54% and 52%, respectively. Safety issues represent about one-third of all the 410 drugs analyzed in Phase I and Phase III studies, versus 17% of all Phase II studies.

Figure 2. Inter-related core aspects for the 'mantra' of R&D for key decisions in drug discovery. Efforts to improve quality of science for drugs and targets, for instance based on translational biology, biomarkers from patients corresponding to a specific target and druggability for candidate drugs, should reduce timelines and cost, and increase the successes in clinical trials.

Figure 3. Evolution and changes of key organizations versus NMEs (new molecular entities). From 1930 to 1960 the increase of the number of approved NMEs is strongly correlated with the proportional expansion of the organizations; whereas from 1960 to 1980 the number of NMEs increased, and the number of organizations that had obtained NMEs reached a plateau, with few new entries or exits. Starting in the 1980s, prominent change in drug discovery and development was observed. New companies such as start-up companies and biotechnology companies expired and, at the same time, exits were largely caused by consolidation strategies (mergers and

acquisitions) rather than bankruptcies.

Figure 4. Top generic firms, data from [12].

Figure 5. Percentage evolution of new molecular entities (NMEs) in each category of drug class (1999–2013), based on approved first-in-class and follower drugs. Between 1999 and 2008 phenotypic screening was the most successful strategy to find first-in-class drugs, whereas target-based screening was the most efficient at finding follower drugs. From 1999 to 2013 the majority of NMEs had been discovered using a target-based (small molecules and biologics) versus systems-based approach (chemocentric and phenotypic screening).

Figure 6. Crossroad between phenotypic- and target-based discovery strategies and best-in-class and first-in-class to develop new drugs for unmet medical need. All options are theoretically possible. Swinney [51] (green arrow) postulated that the unmet medical need should be tackled via a process based on an iterative increase in knowledge, and the progression to find best-in-class drugs from empirical (phenotypic) to hypothesis (target-based approach) testing.

Figure 7. Main current strategies to find and develop new small molecule drugs. The red arrows represent the classical optimization process or the hit- or lead-finding process.

Figure 8. Potential scenarios of the pharmaceutical science based on Crommelin *et al.* analysis [57]. The matrix shows a global view of the potential scenarios.

Figure 9. Simple overview for new hit, lead and drug optimization process using the space concept strategy (real and virtual) and metrics to qualify chemical entities. The chemical space can be subdivided into four clusters associated with several specific chemical and physicochemical properties or topological descriptors as recognition patterns such as MW, clogP, number of hydrogen acceptors (NHA) and number of hydrogen donors (NHD) to define these discrete areas. Thus, drug-like chemical space (Ro5, oral route, grey cube), lead-like chemical space (Ro4, green cube), fragment chemical space (Ro3, bright blue cube) and one mauve cube dedicated to the Ro5' for transdermal drugs can be represented. Other spaces dedicated to other administration routes can also be used (mauve cube). Inside the Ro5 (clinical candidates), Ro5' (clinical candidates) and Ro4 (leads), the use of the ligand efficiency (LE) as a simple indices or metric to quantify the molecular quality of the different chemical entity types, for selection and optimization inside each cluster. Other indices can be also used such as LLE, BEI/SEI, SIHE or QED. As shown, the optimization navigation process between each cluster can be performed using LE, LLE or BEI/SEI. Based on these metrics, construction of more 'druggable' libraries (from fragments, leads or drugs) can be developed. The overlapping of the drug-likeness chemical space continuum (Ro5, grey cube) and the 3D 'target classes' (block-cylinder, also called target space) including individually, for instance, PPI space, kinase space, G-protein-coupled receptor (GPCR) space etc., defined an overlap volume (green rays, truncated cylinder) for which all the compounds (virtual or real) within this space are druggable; the anti-overlap area corresponds to the poorly druggable compounds. The same parameters used to define the boundaries of druggable compounds (e.g. Ro5) can be used to define a specific target space including drugs.

Table 1. Average of costs and FDA approval times according to drug discovery strategies

	Target-based drug discovery	Phenotypic-based drug discovery	Drug repurposing screen	Target identification by repurposing screen
FDA approval	~10–12 years	~10–12 years	~2–3 years	~4–6 months

Cost	~US\$ 1 billion	~US\$ 1 billion	~US\$ 10 million	~US\$ 100 000
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Figure 1. Clinical failures by clinical trial phases.

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Figure 2. Inter-related core aspects for 'Mantra' of R&D for key decisions in drug discovery.

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Figure 3. Evolution/changes of key organizations (NMEs: new molecular entities).

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Figure 4. Top generic firms, data from ref. 13.

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Figure 5. Percentage of NMEs in each category of drug class (1999 – 2013).

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Figure 6. Cross road between phenotypic- and target-based discovery and best-in-class and first-in-class.

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Figure 7. Main current strategies to find and develop new drugs. The red arrows represent the optimization process or the hit/lead finding process.

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Figure 8. Potential scenarios of the pharmaceutical science.

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