The Drug Discovery and Development Industry in India—Two Decades of Proprietary Small-Molecule R&D

Edmond Differding*[^a]
This review provides a comprehensive survey of proprietary drug discovery and development efforts performed by Indian companies between 1994 and mid-2016. It is based on the identification and detailed analysis of pharmaceutical, biotechnology, and contract research companies active in proprietary new chemical entity (NCE) research and development (R&D) in India. Information on preclinical and clinical development compounds was collected by company, therapeutic indication, mode of action, target class, and development status. The analysis focuses on the overall pipeline and its evolution over two decades, contributions by type of company, therapeutic focus, attrition rates, and contribution to Western pharmaceutical pipelines through licensing agreements. This comprehensive analysis is the first of its kind, and, in our view, represents a significant contribution to the understanding of the current state of the drug discovery and development industry in India.

1. Introduction

In 1997, DRF-2593, later known as balaglitazone, a small-molecule peroxisome proliferator-activated receptor γ (PPARγ) agonist discovered at Dr. Reddy’s Laboratories (DRL) in Hyderabad, became the first preclinical-stage compound discovered at an Indian pharmaceutical company to be licensed to a Western company, Novo Nordisk.\[1\] This deal was hailed by many at that time as the first step on the way to what was expected to become a growing flow of successful drugs from India. However, by 2009, DRL had terminated all its internal discovery activities, without having launched a single new drug.\[6\] This exit from early in-house pharmaceutical research activities followed the one in 2008 by Ranbaxy Laboratories, and preceded by five years the one of a third major Indian company, Piramal Enterprises, in 2014.\[3, 4\] Other Indian companies have abandoned, significantly decreased, or postponed their research efforts in recent years, or are experiencing slow progress, if any, with major pipeline products. Proprietary drug discovery activities in India had been initiated since the mid-1990s by companies that had been active in the generics business, often for several decades. At that time, India was poised to become the drug discovery powerhouse of the world, as it had become its generics pharmacy. We know today that this grand vision did not materialize. But does this mean the end of the drug discovery industry in India, the “Death of a Dream” as some have claimed?\[20\] We think this deserves a more thorough analysis.

Drug discovery and pharmaceutical R&D in India has been reviewed and analyzed previously, but generally from specific points of view, such as its historical background,\[6–8\] the fate of the big pharma companies,\[5, 9\] or the impact of process versus product patent output as a consequence of the Agreement on Trade-Related Aspects of Intellectual Property Rights (the so-called TRIPS agreement).\[10\] Other authors have analyzed its socioeconomic impact and public policy implications and recommendations,\[11–15\] drug development in India and in comparison with other emerging countries,\[16, 17\] drug discovery in private companies and in publicly funded institutions,\[18, 19\] current changes and opportunities,\[20, 21\] or out-licensing deals.\[22\] We recently reviewed contract and collaborative research alliances between Indian and global pharmaceutical companies.\[23\] Although these components represent valuable contributions to the understanding of India’s current pharmaceutical industry environment, they lack a comprehensive analysis of the overall scientific productivity of proprietary drug discovery in India, its ongoing achievements in contributing to the global drug discovery and development pipeline, but also its challenges, the knowledge of which is required if one wants to better understand the country’s current situation.

In this review, we attempt to fill this gap by describing and analyzing in a comprehensive manner the contributions to proprietary drug discovery by Indian companies, and by highlighting how the landscape of industrial pharmaceutical research in India, as we know it today, has evolved from its beginnings over two decades ago, into the current ensemble of pharmaceutical and biotechnology companies.

2. Analysis Data and Methods

In our analysis we aim to cover all proprietary research by Indian companies on new chemical entities (NCEs) that have reached preclinical or clinical development stages between its beginnings in 1994 and mid-2016. We set out by identifying and screening today’s top-100 Indian pharmaceutical and biotechnology companies, as assessed from their latest available annual revenue figures, that is, annual reports of public companies, and various sources for privately held companies (Supporting Information Table 5).\[24–27\] We included former top-100 companies with contributions to drug discovery, that have been acquired since, that is, three companies. These have been complemented by all early-stage companies identified by an extensive analysis of Indian drug development activities. We have included several companies headquartered outside of India, but with Indian founders, and in general discovery and development activities run out of India. Not included in the analysis are Indian subsidiaries of multinational companies, although one company is specifically mentioned in the text for its contributions (AstraZeneca India). We have focused our work specifically on small-molecule drug discovery, and have excluded biologics, vaccines, botanical drugs, herbal extracts,
or combination preparations of existing commercial drugs, and repositioned existing products. Prodrugs or polymer-supported forms of marketed drugs, as well as peptides were only included if they were part of broader NCE drug discovery efforts. Compounds that were in-licensed for clinical development purposes from external sources are mentioned in text and tables as integral part of company backgrounds, although they are not included in calculations nor figures. Not included either are drug discovery projects at Indian academic and public research institutions, unless these were done in collaboration with pharma companies and led to joint patent applications. More comprehensive reports on these have been published elsewhere.\[8, 18, 19, 28–31\]

For each company, we have analyzed annual reports, as available from company websites or from service providers;\[32\] company or investor presentations, web pages, press releases, and published patent applications.\[31\] We have compiled all available information, including, where available, compound codes, therapeutic areas, modes of action, years in which development phases were initiated, highest stage of development reached, current status of development, and eventually status of partnerships or licensing deals with global pharmaceutical companies. Our analysis reflects the status of the drug discovery pipeline in India by mid-2016.

Several clarifications and limitations regarding our approach are noteworthy at the outset. First, companies were identified based on their publicly disclosed scientific output in terms of development compounds or patent applications. Although we are confident to have included all relevant companies and compounds in our analysis, we cannot exclude minor omissions. Should this be the case, the overall impact on our analysis would be small, given the large number of companies and compounds included in this review.

Second, timelines were assessed based on the years during which the information was disclosed. As this includes annual reports, actual decision dates can be offset by up to a full year. Further, as the term “preclinical” can represent stages from early research to preclinical studies enabling Investigational New Drug (IND) applications, we have made efforts to include only compounds beyond the early discovery stage, that is, our inclusion criteria have been stricter than in an earlier preliminary short report.\[34\] Also, as the termination of development is not always publicized, we assumed it occurred during the year in which the compound disappeared from company reports or presentations.

Finally, although considerable efforts have been made to identify all relevant documents, limitations in the amounts of publicly available information, and time-lags between conducting research and disclosing the results publicly, means that some projects might not have been captured correctly in our analysis. Despite these limitations, we strongly believe the data presented provides valuable information, as it gives for the first time a comprehensive view over two decades of proprietary Indian pharmaceutical R&D.

3. Drug Discovery in India

3.1. Historical background

India’s oldest pharmaceutical companies were established at the turn of the past century, such as Bengal Chemicals & Pharmaceuticals Ltd. (1901), or Alembic Chemical Works (1907) to manufacture quality chemicals, pharmaceuticals and home products.\[12\] The beginning of drug discovery in the country can be traced back to the second decade of the twentieth century, with work on drugs for visceral leishmaniasis, also known as kala-azar, by Upender Nath Brahmachari at the Campbell Medical College, Calcutta, one of the oldest medical schools to teach European medicine in India, which led to “urea stibamine”, introduced in 1922.\[8, 13\] The drug was designed to decrease the toxicity of known inorganic pentavalent antimony salts by their incorporation into organometallic aniline derivatives, inspired by Ehrlich’s salvarsan, an organoarsenic compound for the treatment of syphilis, that had been introduced in 1910. Urea stibamine was only the second successful anti-infective agent to be developed in the world, saved countless patients in the 1920–1930s, and paved the way for the development of more recent antimonials such as sodium stibogluconate, or meglumine antimoniate, both on the World Health Organization (WHO) list of essential medicines.\[15, 36\] Although not a drug, oral rehydration therapy (ORT), that is, drinking water with controlled amounts of salt and sugar, considered as “potentially the most important medical advance of the [20th] century”,\[37\] was first discovered by H. N. Chatterjee, a medical practitioner working on cholera patients in Calcutta. Despite being published 1953 in The Lancet, it was unfortunately ignored, only to be rediscovered in 1968 by Western scientists.\[18\]

During the early years after independence, the Government of India, through its Council of Scientific and Industrial Research (CSIR), established the Central Drug Research Institute (CDRI) in Lucknow to lead the country’s efforts in drug research and development (1951).\[8, 39, 40\] followed later by other public institutions such as the Regional Research Laboratories in Hyderabad (1956, now Indian Institute of Chemical Technology, IICT),\[41\] and in Jammu (1957, now Indian Institute of Inte-
CDRI’s main focus was to identify lead molecules for tropical diseases and population control measures from medicinal plants, initially relying on the country’s traditional systems of medicine such as Ayurveda and Unani, but later expanded to include other plants, and synthetic small molecules. The knowledge of ayurvedic remedies resulted in a number of drugs or standardized extracts with identified active compounds: “gum guggul”, derived from Commiphora mukul, led to the identification of guggulsterones, antagonists of the farnesoid X receptor (FXR) receptor with lipid-lowering properties, approved 1986 in India as an extract under the name Gugulipid. “brahmi”, prepared from Bacopa monnieri, gave triterpenoid glycoside modulators of the serotonin system as memory enhancers, launched in 1996 as a standardized extract under the name Memory plus. The search for antimalarials, based on the investigation of Artemisia annua, used in traditional Chinese medicine, resulted in arteether, a drug able to cure multidrug-resistant or chloroquine-resistant Plasmodium falciparum, approved in 1998.

Further research efforts in India to discover new drugs from plants have been reviewed recently. Small-molecule drug discovery, centchroman (ormeloxifene), a selective estrogen receptor modulator, and the world’s first nonsteroidal oral contraceptive, introduced in 1990, remains among CDRI’s major achievements. The institute’s current challenges such as a decrease in the output of new drugs have been discussed recently, and potential opportunities include the revival of natural products chemistry, re-emphasizing phenotype assays, and strengthening mode of action and target identification capabilities. Notable discoveries made at other public laboratories are enfenamic acid, an anti-inflammatory agent (IICT, 1980), or more recently risorin, a combination preparation for tuberculosis (IIIM, 2009). A list of projects toward drug discovery research at additional CSIR-funded institutions is available at the Council’s website.

In these early years, the pharmaceutical industry as a whole, including during the two decades after India’s independence, was dominated by multinational companies, that imported their bulk products, even after the setup in 1960 of public sector companies, such as Hindustan Antibiotics Ltd., and Indian Drugs and Pharmaceuticals Ltd. Notable discoveries made by multinational companies in India were for example reserpine, an indole alkaloid with antipsychotic and antihypertensive properties isolated from Rauwolfia serpentina at the Ciba Research Centre in Mumbai (then Bombay, 1952), forskolin, a diterpenoid adenylylate cyclase activator (1974), discovered independently as colonel at CDRI, and flavopiridol, the first cyclin-dependent kinase inhibitor, derived from the natural product rohitukine (1990s), both at the Hoechst Bombay Research Centre.

This changed radically with the Indian Patent Act of 1970, which abolished product patents for pharmaceutical ingredients, recognizing only patents with a decreased term (5–7 years) for process improvements (also called reverse engineering, allowing to copy foreign patented drugs), which was much less challenging than innovative drug discovery. The ensuing rise of local competitors, the loss of royalties from product patents, and new laws limiting the price of certain drugs, as well as decreasing the ownership of multinational companies in their Indian enterprises to a maximum of 40%, led most multinational companies to leave India. This all strengthened the growing local generics industry, which became “the world’s pharmacy”, according to Médecins Sans Frontières (or Doctors Without Borders) accounting currently for 10% of the global pharmaceutical production, and 20% of global exports of generics in volume terms.

India’s “New Economic Policy” of 1991, aiming to liberalize the country’s economic policies, and its joining the World Trade Organization (WTO) in 1995, which included the signature of an agreement on TRIPS, with a ten year transition period from 1995 to 2005, and the Indian Patents (Amendment) Act 2005, opened the country again to product patents, and consequently to pharmaceutical innovation. The main industry players recognized the unique opportunities offered by these changes.

To reflect the significant changes that the entire industry went through over two decades, we have chosen to present our data by company in a chronological order, starting with the large Indian pharma companies that were the first to enter the field (Table 1). These were followed by contract research organizations (CROs), a limited number of which initiated also proprietary projects, and more recently, by biotechnology and startup companies specializing in integrated proprietary drug discovery.

3.2. Initiation of drug discovery at large pharmaceutical companies

Dr. Reddy’s Laboratories (DRL), established in 1984 for the manufacturing of active pharmaceutical ingredients (APIs), and with over 21 000 employees worldwide, had been the first Indian company to launch drug discovery research in 1994. Between 1995 and 2009, DRL reported 27 development compounds, of which 12 reached the clinical development stage (Supporting Information Table 6a, entries 1–27). It was the first Indian company to out-license, in 1997, a molecule, balaglitazone 1 (DRF-2593), a thiazolidinone (or glitzaone)-type PPARγ agonist for the treatment of diabetes, and in 1998 a second molecule, ragaglitazar 2 (DRF-2725), a dual PPAR α/γ insulin sensitizer for metabolic disorders, to a Western company, Novo Nordisk (Figure 1). Novo Nordisk eventually abandoned 2 in 2002, when bladder tumors were identified in rats during toxicology studies, and returned 1 to DRL in 2004. In 2005 DRL partnered with Rhesciences for the further development of 1, which in 2007 became the first Indian compound to reach the level of Phase 3 studies and were completed with DRL’s internal funds. Although positive clinical data were reported in 2010, the compound was abandoned in 2011, after Avandia (rosiglitazone), another compound of the glitazone family developed by GlaxoSmithKline (GSK), had been linked to apparent risks for increased heart attacks, and banned from use in Europe and India in 2010. DRL found additional partners in Novartis (2001) for the development of DRF-4158, a dual PPARα/γ agonist and hydroxymeth-
Figure 1. Examples of development compounds.
In 2005, a joint venture led to the creation of Perlecan Pharma, with the aim to develop four DRL compounds: RUS-3108, a perlecan inducer for the treatment of atherosclerosis,[36] DRL-10945, a non-fibrate predominantly PPARα agonist for the treatment of metabolic disorders,[37] DRL-11605 a pan-PPARα/β/γ agonist for the treatment of obesity and dyslipidemia,[38] and DRL-16536, an AMP-activated protein kinase (AMPK) modulator for metabolic disorders.[39] All four compounds failed in preclinical or early clinical studies and were subsequently abandoned. In 2008, the joint venture was terminated, and DRL had to buy back the shares. The company entered into a collaboration with Argenta Discovery to develop novel treatments for chronic obstructive pulmonary disease (COPD), which led in 2007 to a clinical development compound,[40] a PPARγ agonist, which was, however, abandoned the following year. Other compounds reached the clinical development stage at DRL, and all failed, including a second camptothecin derivative, DRL-1644,[41] (abandoned in 2005), and two compounds with an undisclosed mechanism of action for the treatment of dyslipidemia, DRL-21994 and DRL-21995.[42] Fourteen more compounds did not pass the preclinical development stage.[43] After these repeated failures, DRL announced in 2009 the closure of its research activities in Hyderabad, shifting its R&D focus to new drug delivery systems, improved generics and biosimilars.[44] The company continued limited development activities, including on DRL-17822, an orally active cholesteryl ester transfer protein (CETP) inhibitor for the treatment of dyslipidemia,[45] which was, however, abandoned in 2013 in Phase 2.

Ranbaxy Laboratories, since 2015 part of Sun Pharma, was established in 1961, and employed more than 14,000 people in 2014.[46,47] The decision in the early 1990s to become a research-based company led to the establishment of a new research center, and to the start of drug discovery projects in 1995, which grew to 280 scientists in 2008.[48] The company’s first proprietary molecule RBx-2258 (parvosin) 4,[49] 5 an adrenergic α1 receptor antagonist for the treatment of benign prostatic hyperplasia, reached clinical Phase 1 stage in 1999 (Supporting Information Table 6a entries 28–43). In 2002, Ranbaxy licensed out 4 to Schwarz Pharma, but the compound was stopped shortly after in Phase 2 development due to unconvincing clinical results. In 2003, Ranbaxy partnered with Medicines for Malaria Venture (MMV) for the development of arotelane or OZ277, subsequently called RBx-11160, for the treatment of Plasmodium falciparum malaria, and was subsequently granted a worldwide license (Supporting Information Table 6b, entry 1).[50,51] The compound reached the Indian market in April 2012 as Synriam, a combination of arotelane maleate and piperazine phosphate, the first medicine developed (although not invented) by an Indian company.[52] In 2003, Ranbaxy signed a deal with GlaxoSmithKline (GSK) for the discovery of treatments for respiratory diseases, which led to RBx-10017609, a dual matrix metalloproteinase-9 and -12 (MMP-9/MMP-12) inhibitor,[53] which reached Phase 2 clinical studies, but has been abandoned since. In 2007, Ranbaxy out-licensed its HMG-CoA reductase inhibitor RBx-10558 8 to Pharmaceutical Product Development (PPD) for the treatment of hypercholesterolemia.[54] PPD, and subsequently its spin-off Furiex undertook clinical studies, but further development of the compound was abandoned in 2011 due to lack of efficacy in Phase 2 studies.[55] In 2008, Ranbaxy partnered with Merck Sharp and Dohme (MSD) for the development of antibacterials and antifungals, but the deal was called off in 2011. Ranbaxy’s discovery group produced other proprietary molecules in a variety of therapeutic areas which reached the stage of clinical development: RBx-4638 or clairnast,[56,57] a very late antigen-4 (VLA-4) antagonist to treat asthma and COPD; RBx-7644 (ran-bezolid) 6, an oxazolidinone-type protein synthesis inhibitor against bacterial infections,[58] RBx-7796 7, a 5-lipoxygenase (5-LO) inhibitor against asthma and allergic rhinitis,[59,60] and RBx-9841, a muscarinic acetylcholine M3 receptor inhibitor against urinary incontinence.[61] Nine additional compounds were stopped at the preclinical development stage. In mid-2008, however, Daichi-Sankyo acquired a majority stake in Ranbaxy, which led to the termination of in-house research projects. In 2015 Daichi-Sankyo sold the generics business of Ranbaxy to Sun Pharma, and in January 2017 decided to close the remaining R&D site in Gurgaon.[62,63]
120038,\textsuperscript{[89]} 11 entered preclinical toxicology studies in 2008, although no further progress has been reported since.

**Wockhardt Ltd.**, headquartered in Mumbai, was founded in 1967, and manufactures and markets generics and biosimilars with currently about 10,000 employees.\textsuperscript{[32, 90]} The company initiated drug discovery in 1997, focusing on treatments for bacterial infections, and brought 15 compounds into development, including salts and single enantiomers, of which five progressed into the clinic (Supporting Information Table 6a, entries 50–64): WCK-771 or levonadifloxacin 13,\textsuperscript{[89]} an oral amino acid ester pro-drug of WCK-771 in Phase 2 in India; WCK-1152 14,\textsuperscript{[91]} also a fluoroquinolone (abandoned); WCK-4873 or nafithromycin, a keta-lide-type protein synthesis inhibitor completed Phase 1 studies in 2015 in the US,\textsuperscript{[89, 94, 95]} and WCK-5107 (or zidebactam 15, a dual penicillin-binding protein 2 (PBP2) and \(\beta\)-lactamase inhibitor).\textsuperscript{[94]} Five compounds or combination preparations received recently the qualified infectious disease product (QIDP) status,\textsuperscript{[94]} which allows fast-track development and review of the drug application by the US Food and Drug Administration (FDA), and is granted to drugs acting against pathogens which have a high degree of unmet needs, such as methicillin-resistant \textit{Staphylococcus aureus} (MRSA).

**Piramal Enterprises Ltd.**, as the company has been known since 2012, was established in 1988 as Nicholas Piramal India Ltd., and entered drug discovery research in 1998 with the acquisition of the Hoechst Research Centre in Mumbai.\textsuperscript{[32, 97]} Piramal’s R&D activities, focusing on oncology, inflammation, metabolic disorders and infections, grew to over 460 scientists in 2012, of which 360 were in NCE discovery research. The company filed its first patent application in 2002 on inhibitors of cyclin-dependent kinases (CDK) for the treatment of cancer, and in 2005 initiated its first clinical Phase 1 studies on P276 (rivaciclib) 16,\textsuperscript{[94]} a novel CDK4 inhibitor, terminated in 2013 after a setback in Phase 2 clinical trials (Supporting Information Table 6a, entries 65–80). P1446 or voruciclib 17,\textsuperscript{[94]} a second CDK4 inhibitor, entered clinical development in 2008. In January 2007 Piramal announced a collaboration with Eli Lilly & Co. on the preclinical and clinical development of two in-licensed Lilly development candidates for the treatment of metabolic disorders: P1201 (mode of action not disclosed) entered Phase 1 in Europe, was stopped in 2013,\textsuperscript{[97]} and P2202, a 11\(\beta\)-hydroxysteroid dehydrogenase type 1 (\(\beta\)HSD1) inhibitor, which entered Phase 1 in Europe in 2009, reached Phase 2 in India and Canada, but has been abandoned since (Supporting Information Table 6b entries 2–3).\textsuperscript{[97]} In 2007, Piramal engaged in an integrated oncology drug discovery collaboration with MSD to discover and develop novel treatments for cancer up to clinical proof-of-concept studies, which led to PL2258,\textsuperscript{[99, 101]} an oral insulin-like growth factor 1 receptor (IGF1R) inhibitor, structurally possibly related to sulfonil-indole derivatives which reached Phase 1,\textsuperscript{[102]} but which has probably been abandoned in 2014. A second IGF1R project (“Target Y”) did not pass the candidate selection stage. Piramal’s natural products collection, with more than 53,000 microbial strains and 7,300 plants and extracts (2011 figures) from diverse habitats,\textsuperscript{[94]} has been made available for screening to external partners, of which two, Pierre Fabre and Oncotest, have been disclosed publicly.\textsuperscript{[103, 104]} In addition to five compounds which were abandoned in preclinical studies, several other Piramal compounds entered clinical trials: P1736 18, a non-thiazolidinedione insulin sensitizer for the treatment of diabetes, discovered using phenotypic screening;\textsuperscript{[105]} P196A, a dual CDK4/\textit{HIF1\(\alpha\)} inhibitor completed Phase 1 in 2013;\textsuperscript{[96]} P3914, a dual-action naproxen-based cyclooxygenase inhibitor linked to an NO donor for the treatment of pain;\textsuperscript{[101]} P7170, or panulisib 19,\textsuperscript{[109, 110]} a phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) and \(\alpha\)-kinase inhibitor for the treatment of cancer and inflammation, partnered with MSD; P7435,\textsuperscript{[93]} a potent and highly selective, oral diaocyglycerol \(\alpha\)-acyltransferase 1 (DGAT1) inhibitor for the treatment of diabetes; and P11187,\textsuperscript{[97]} a G-protein-coupled receptor 40 (GPR40) agonist against metabolic disorders. After a name change to Piramal Healthcare Ltd. in 2007, the company evolved rapidly over the following years, by selling in 2010 its generics business to Abbott, by acquiring in 2011 Oxycon Healthcare for drug discovery services, rebranded as Piramal Discovery Solutions, and in 2012 Bayer’s molecular imaging development portfolio which became Piramal Imaging.\textsuperscript{[97]} In August 2014, Piramal announced the closure of its drug discovery activities in Mumbai, essentially terminating all early-stage R&D activities, affecting close to 200 scientists.\textsuperscript{[111]} An attempt was made to out-license the five at that time remaining Phase 1 compounds, but most were later abandoned, and only the DGAT1 inhibitor and the GPR40 agonist completed Phase 1 studies in 2014, although no further information has been published.\textsuperscript{[97]} Two early candidate compounds were licensed to Kirish Biotech in 2015 (see below).

**Dabur Research Foundation (DRF)** was incorporated in 1979 as the healthcare R&D branch of Dabur, a company active in ayurvedic medicines and consumer goods in India since 1886. DRF established preclinical labs in 1994, and initiated drug discovery research in 1998.\textsuperscript{[32, 112]} The company filed a series of patent applications in 2000 on the use of neuropeptide analogues for the treatment of cancer, but did never develop a proprietary NCE, as DRF-7295,\textsuperscript{[113]} Dabur’s first so-called NCE, was actually a mixture of peptides derived from vasoactive intestinal peptide (VIP), bombesin, substance P and somatostatin, known to be overexpressed in various cancers, which entered Phase 1 clinical trials as a potential anti-cancer vaccine in India in 2002, followed by reportedly successful Phase 2 trials initiated in 2004. However, no progress has been reported since 2008, and it has most likely been abandoned. When in 2008 Fresenius Kabi acquired Dabur Pharma, the Dabur Research Foundation was spun out and
Zydus Cadila Healthcare (or Cadila Healthcare), the pharmaceutical arm of what became known as the Zydus Cadila group, headquartered in Ahmedabad, was initially founded as Cadila Laboratories in 1952, and was incorporated in 1995 after separating from Cadila Pharmaceuticals (see below). The company had over 15,000 employees worldwide in 2016, with operations in generics, active pharmaceutical ingredients, animal healthcare products, as well as R&D in the areas of NCEs, formulation, biosimilars and vaccines. The Zydus Research Centre, established in 2000 in Ahmedabad, houses around 400 scientists, out of which about 250 dedicated to NCE research. Zydus Cadila initiated its NCE discovery programs in 2000 with a strong focus on metabolic disorders and, to a lesser extent, inflammatory diseases, and disclosed a total of 15 drug candidates, of which 13 moved into clinical development stages (Supporting Information Table 6a, entries 89–103). ZYH1 (INN saroglitazar, trademark Lipaglyn) was approved for the treatment of diabetic dyslipidemia in 2013 in India as the first NCE discovered and developed by an Indian company. It is currently undergoing Phase 1 studies for the treatment of diabetic nephropathy (HIF-PH) inhibitor for the treatment of anemia, commonly observed in chronic kidney disorder. In addition, ZYTP1, a poly(ADP-ribose) polymerase (PARP) inhibitor has recently been approved for the initiation of Phase 1 trials in India. Nine additional compounds progressed into clinical studies, but most were abandoned during Phase 1 studies. The majority focused on treating diabetes via different modes of action: ZHY2, a dual PPARα/γ agonist; ZYO1, a cannabinoid receptor type 1 (CB1) receptor antagonist, stopped in Phase 2; ZYD1, a peptide GLP-1 agonist; ZYOG1, an oral peptideidomimetic GLP-1 agonist; ZYGK1, a glucokinase activator; and ZYG19, a G-protein-coupled receptor 119 (GPR119) agonist. Others targeted dyslipidemia (ZYT1, a thyroid hormone receptor β (TR-β) agonist), inflammation and pain (ZY11, mode of action not disclosed, abandoned in Phase 2), or osteoporosis (ZYPH0907, an oral parathyroid hormone (PTH) receptor agonist). The company also entered several collaborative drug discovery alliances, including with Karo Bio on inflammatory disorders (2008) which led to a patent application, and Lilly on cardiovascular disorders (2009). Although both collaborations have been terminated since.

Cadila Pharmaceuticals, the privately owned sister company of the parent company’s split-up into two separate entities in 1995, has been considerably less involved in NCE research. It developed for example, Polycap, a fixed-dose combination treatment based on existing drugs to treat heart attacks, Mycidac-C, a lung cancer vaccine, or Risorin to treat tuberculosis with a combination of rifampicin and piperazine, an alkaloid extracted from pepper whose bioavailability enhancing properties had been discovered at the Regional Research Laboratory, now Indian Institute of Integrative Medicine (IIIM), Jammu. The company also engaged in preclinical and clini-
FDC Ltd. manufactures and sells APIs and formulations, and initiated efforts in R&D around 2000, focusing on academic collaborations, in particular with the National Chemical Laboratory (NCL) in Pune, on antifungals, which has led to a series of joint patent applications, including on Fluconazole analogues.[32,149-152] No progress, however, has been reported on NCL-FDC-101, an early-stage compound disclosed in 2006, which is likely to have been abandoned, as no reference has been made to drug discovery in annual reports since 2013 (Supporting Information Table 6a, entry 104).[149]

JB Chemicals & Pharmaceuticals Ltd. (JBCPL), a producer of generics and bulk drugs established in 1976, initiated NCE research around the year 2000, working on NSAIDS including cyclooxygenase-2 (COX-2) inhibitors for the treatment of inflammation.[32,153-155] In 2004 the company reported three compounds in preclinical development, including JB-7/G (Supporting Information Table 6a, entry 105).[150] In the same year, however, work on COX-2 inhibitors was badly affected worldwide by the withdrawal by MSD of rofecoxib (trademark Vioxx) due to the increased risk of cardiovascular side effects, and development of JB-7/G was discontinued. JBCPL abandoned NCE drug discovery subsequently, as no further research projects have been mentioned in annual reports, and no further NCE patents have been filed since 2006.

Cipla Ltd., founded in 1935, is the world’s largest manufacturer in terms of volume of antiretroviral drugs to fight HIV.[157] The company did not invest in internal NCE research, but licensed two compounds for commercialization from Central Drug Research Institute (CDRI), that is, gugulipid to treat hyperlipidemia (1987),[158] and chandomion iodide, a neuromuscular blocking agent (1994).[8] A collaboration around the year 2000 with University of Mumbai led to patents on antihistamines,[158] and antibacterials,[159] but these compounds were abandoned later, without any information being disclosed on their development status. Cipla invested in stem cell research in 2010 through a strategic alliance with Stempeutics Research, and in 2014 launched its business-incubating unit, Cipla New Ventures, through which it invested in Chase Pharmaceuticals Corporation, an early-stage US-based development company, to finance Phase 2 studies of the company’s lead Alzheimer’s disease (AD) treatment drug CPC-201.[160]

Glenmark Pharmaceuticals, was founded in 1977 for the manufacturing of APIs and generics, and employs over 12,000 people.[32,161] In 2001, the company initiated small-molecule drug discovery in the in newly established R&D center in Navi Mumbai, focusing with currently around 300 scientists on metabolic disorders and airway diseases, and in 2004 inaugurated its biologics research center in Switzerland,[32,161] with currently 50 researchers. Glenmark’s small-molecule research has delivered so far 19 development compounds, of which eight moved into clinical trials, including several phosphodiesterase type 4 (PDE4) inhibitors for airway diseases (Supporting Information Table 6a, entries 106–124).[162] One of these, oglemilast (GRC-3886)[163,164] was Glenmark’s first compound to be out-licensed, to Forest Laboratories in 2004 for the North American market, followed in 2005 with Teijin for Japan. In 2009 the compound was abandoned in Phase 2. Glenmark has been successful in out-licensing the rights to further compounds: to Merck KGaA in 2006 for melogliptin (GRC-8200)[24,165,166] a DPP-IV inhibitor for type 2 diabetes, which was abandoned after Phase 2 studies in 2011; to Lilly in 2007 for GRC-6211[25,167,168] a transient receptor potential cation channel type V1 (TRPV1) antagonist for various diseases, stopped in Phase 2 studies the following year; more recently, to Sanofi in 2010 for GRC-15300 (or SAR292833), globally the first transient receptor potential cation channel type V3 (TRPV3) antagonist to enter clinical trials, for osteoarthritis pain.[169,170] In 2012 Glenmark signed an option agreement with Forest Laboratories for the discovery and development of novel microsomal prostaglandin E synthase-1 (mPGES1) inhibitors for the treatment of chronic inflammatory conditions, with GRC-27864 currently in Phase 1.[171-174] Additional compounds which reached the clinical stage are revamistat (GRC-4039)[26,175,176] also a PDE4 inhibitor, stopped in 2012 at the Phase 2 stage; tedalibin (GRC-10693) [27,177,178] a cannabinoid CB2 receptor agonist for the treatment of inflammatory and neuropathic pain (abandoned in Phase 1 in 2011); and GRC-17536,[179] a transient receptor potential cation channel, subfamily A, member 1 (TRPA1) inhibitor for respiratory disorders, that reached Phase 2 studies,[180] exploring a potassium salt and prodrugs. Glenmark also actively in-licensed development compounds for the markets in India and other emerging countries. This includes, in 2005 Napo Pharmaceutical’s anti-idiopathic profuse cefuroxime, a purified oligomeric proanthocyanidin (M, up to 9 kDa) which blocks two unrelated chloride channels in the gut, approved in 2012,[23] or monoclonal antibodies to build up a biologics pipeline (Supporting Information Table 6b entry 4).[161]

Lupin Ltd., founded in 1968, is one of the world’s largest producers of generic antituberculosis drugs with more than 16,000 employees worldwide.[32,181] Lupin opened its R&D center in 2001 in Pune, with a focus on NCE drug discovery, process chemistry for generics, research in dosage forms, and advanced drug delivery systems. Lupin’s first therapeutic focus was broad and included cardiovascular (antimigraine), anti-infectives (antituberculosis, bacterial resistance), respiratory (asthma) and dermatological (psoriasis) diseases. The company invested significantly into the development of herbal drugs, and claims to have identified the active constituent of Desoris, a purified arabinogalactan–protein molecule code-named LL-4218 (desoside-P)[182] which was brought into Phase 2 (Supporting Information Table 6a, entries 125–131). Two further molecules were abandoned: sudoterb (LL-3858)[28,183,184] a novel small-molecule antibacterial agent that completed Phase 2 studies in India in late 2013, and LL-6531, a preclinical stage PPAR modulator.[181] Lupin’s R&D was entirely restructured in 2010, with the launch of new projects in the therapeutic areas of metabolic and endocrine disorders, pain and inflammation, autoimmune diseases, central nervous system (CNS) including cognition deficits, oncology and antivirals. In 2015 the company’s R&D department counted over 300 scientists, of which an estimated 130 in NCE drug discovery. Among the new projects, four are undergoing clinical development in...
European countries,[181] and are available for out-licensing: LND101001, a Phase 2 α7 nAChR modulator for cognitive deficits such as in AD,[184,146] LNP1892, a Phase 1 calcium-sensing receptor (CaSR) modulator for the treatment of primary hyperparathyroidism,[187] LNP3794, a mitogen-activated protein kinase kinase (MEK) inhibitor, which completed a Phase 1 study in terminally ill patients in the UK,[188] and LNP1955, a calcium release-activated channel (CRAC) modulator for the treatment of autoimmune diseases such as rheumatoid arthritis and psoriasis, which has successfully completed Phase 1 studies, and is entering Phase 2 proof-of-concept studies.[189]

Reliance Life Sciences was established in 2001 as the bio-pharmaceutical arm of Reliance Industries, one of India’s largest industrial conglomerates.[190] In addition to working on stem cell technologies, since 2002, the company filed patent applications from 2005 to 2007 on small-molecule compounds to treat lipase-mediated diseases, inflammation and cancer.[191–193] These included early-stage compounds such as RSLC-0409, a glucosidase,[194] or RSLC-0520, a phanethrene derived from *Euplopha ochratae*,[195] both inhibiting Toll-Like receptor (TLR) signaling pathways (Supporting Information Table 6a, entries 132–133). The compounds are likely to have been abandoned around 2010 when the company’s research focus shifted to siRNA-mediated approaches to treat cancer.[196]

Orchid Chemicals & Pharmaceuticals, or Orchid Pharma since its recent name change in 2015, was established in 1992 in Chennai to manufacture antibiotics, and entered drug discovery in 2001 with projects in the areas of anti-infectives and treatments for pain.[32,197] In 2002, the company engaged in a joint venture to develop US-based firm Bexel Biotechnology’s BLX-1002, an oral, non-PPAR AMPK activator for the treatment of diabetes,[198] later repositioned for NASH (2012), but no further progress has been reported recently.[197] In 2008, Orchid invested in Diakron Pharmaceuticals, a US-based company that had an exclusive license to MSD’s investigational oral anticoagulant drug, a direct thrombin inhibitor later known as DPOC-4088 (or DP-4088),[199] which reached Phase 1 clinical studies in Europe in 2012 (Supporting Information Table 6b, entries 5–6).[200] The company’s own internal discovery efforts have a broad therapeutic focus, covering infectious diseases, inflammation, pain, oncology, metabolic disorders, and CNS diseases. OCID-2987,[197,201] a PDE4 inhibitor for the treatment of inflammatory disorders such as COPD, completed successfully Phase 1 studies in Europe in 2012, and OCID-4681 29[202,203] a histone deacetylase inhibitor (HDAC) inhibitor for cancer that had received approval in 2011 for Phase 1 studies for solid tumors in India, but we assume both have been abandoned, as cancer and inflammation are not mentioned in the company’s latest annual reports.[197] Two additional compounds were abandoned at the preclinical stage: OCID-5005, a STAT-3/IL-6 inhibitor for oncology, and a unnamed Th1/Th2 cytokine synthesis inhibitor for inflammation (Supporting Information Table 2a, entries 134–138).[197] Financial issues led Orchid, as of 2009, to sell parts of its business to Hospira (now part of Pfizer). As a consequence, no progress has been reported on its discovery programs since 2010, and no further NCE patent application has been published since 2012. However, in 2013 Orchid licensed its broad-spectrum β-lactamase inhibitor OCID-5090, a zwitterionic N-methylated tozobactam derivative, to the German Allecra Therapeutics for a 20% stake in the company, for use in combination with antibiotics to treat multidrug-resistant gram negative bacteria.[204–207] Allecra’s lead compound AAI202, a combination of cephefim and AAI101/OCID-5090 30, is currently in Phase 1 studies in France.[206,209]

Suven Life Sciences Ltd., incorporated in 1989 as Suven Pharma, with the goal to offer contract research and manufacturing services, changed its name in 2003, the year it initiated internal drug discovery efforts, focusing exclusively on the central nervous system (CNS).[32,210] The company entered into a global collaborative research partnership in 2006 with Eli Lilly, followed by a second deal in 2008, although nothing has been disclosed on the outcome of this collaboration.[211] Suven filed its first IND application in 2007 for lead compound SUVN-502, a serotonin 5-HT 3 receptor antagonist for the treatment of mild cognitive impairment associated with CNS diseases such as AD, Parkinson’s disease (PD) or schizophrenia. Phase 1 studies were completed in 2009, and after unsuccessful attempts to out-license the compound, Suven initiated Phase 2a trials on its own in 2015 (Supporting Information Table 6a, entries 139–153),[212–214] SUVN-G3031, a histamine H 3 receptor antagonist for cognitive impairment completed Phase 1 studies in 2015 in the US,[212,215] SUVN-D4010, a partial SHT 3 agonist for the same indication entered Phase 1 trials in the US in 2015,[212,216] Preclinical stage compounds include α4/β2 nAChR antagonists such as SUVN-911, or cannabinoid CB 2 receptor agonists.[212,217]

Natco Pharma was incorporated in 1981 with the objective to manufacture conventional and controlled release generics, and inaugurated in 1997 the Natco Research Centre (NRC) in Hyderabad.[218] In 2003 Natco launched its oncology division with generic imatinib (Gleevec), and initiated in-house discovery research, with a first patent filing in 2004 on Bcr-Abl kinase inhibitors. In 2012 Natco was awarded the first Indian compulsory license for Bayer’s and Onyx Pharmaceuticals’ sorafenib. The company has currently two compounds in clinical development: NRC-AN-019 31,[219] an analogue of imatinib, which received orphan drug status for chronic myelogenous leukemia (CML), glioma and pancreatic cancer in 2011 by the FDA (undergoing Phase 2 trials in India), and NRC 2694 32,[220] an erlotinib (Tarceva) analogue EGFR kinase inhibitor in Phase 1 trials in India for late-stage solid tumors (Supporting Information Table 6a, entries 154–155). NRC-AN-015, an earlier Bcr-Abl tyrosine kinase inhibitor, has been abandoned at the preclinical stage.[218]

Panacea Biotec, founded 1984, has become one of the top-10 vaccine producers in India, in addition to manufacturing APIs, and the marketing of generics.[221] The company has notably played a key role worldwide in polio eradication campaigns. It currently counts around 2500 employees, down from 3300 in 2014, of which 230 were in R&D. It has four R&D centers, including the LAKSH Drug Discovery R&D Centre in Mohali, Punjab, established in 2005 focusing on metabolic disorders, diabetes and infectious diseases. In 2007 CNS diseases were added as an indication through a collaboration with
Punjab University, and the NCE discovery group grew to over 100 people in 2011. The company started filing NCE patents as of 2008, in particular on inhibitors of DPP-IV and of sodium-glucose co-transporter-2 (SGLT2) for the treatment of diabetes, and on novel oxazolidinone antibacterial agents to treat infectious diseases. Its research efforts have led to four development compounds, of which PBL-1427, a DPP-IV inhibitor reached Phase 1 clinical trials in India in 2012 (Supporting Information Table 6a, entries 157–160).[222,223] Panacea’s turnover in fiscal year 2014–2015 decreased to less than half of what it was in 2010–2011, after the company was hit by quality management issues with its vaccine manufacturing. As a consequence of the severe drop in income, internal R&D was decreased, in-house drug discovery was halted, and attempts were made to out-license or partner existing internal projects. In 2014 the company adopted a new, integrated contract research service model under the brand name of Panacea Life Sciences. Panacea’s current pipeline includes, in addition to PBL-1427, one additional unnamed compound at the preclinical stage.[224]

Matrix Laboratories was set up in 2000 to manufacture generic APIs, and grew by domestic and international acquisitions to become in 2006 ranked 10 of Indian pharmaceutical companies in terms of market capitalization.[32,222] At the end of 2004, Matrix signed a collaboration agreement with aRigen, a Japanese biotech company focusing on anti-infectives research, to supply compounds for screening. During the following year, the company initiated internal drug discovery programs targeting asthma and metabolic disorders, later expanding into treatments of pain. Matrix’s first patent applications were filed in 2006 on DPP-IV inhibitors, with the lead compound MX-6001, and phosphodiesterase (PDE) inhibitors, including PDE4 inhibitor MX-4007, followed in 2008 on vanilloid receptor modulators (Supporting Information Table 6a, entries 161–162).[225–228] In 2006, Matrix, at that time with 2000 employees, of which 200 scientists in R&D, was acquired by Mylan. Drug discovery and development was subsequently abandoned, and did not appear in later annual reports of the company.

Hetero Drugs is one of the top-10 pharmaceutical companies, and the largest privately held Indian pharmaceutical company.[229] Founded in 1993, with currently over 15,000 employees, it is the world’s largest manufacturer of antiretroviral drugs, accounting for a 25% share of the global antiretroviral production. Hetero Research Foundation (HRF), the R&D arm of the Hetero Group companies, employs 400 scientists focusing on process and analytical R&D, and more recently on discovery research. The company’s main areas of discovery, initiated around 2006 include treatments against human immunodeficiency virus (HIV), hepatitis C virus (HCV), cancer and diabetes. HRF has been particularly active in anti-HIV drug discovery, where it started filing patents in 2008 on compounds with different mechanisms of action, including nucleosides,[230] peptidomimetic protease inhibitors,[231] and more recently on triterpene maturation inhibitors.[232] In 2012 HRF claimed to have two novel compounds ready to enter Phase 1 clinical studies (Supporting Information Table 6a, entries 163–164).[233] However, no information has been publicly disclosed on the progress of these compounds.

Jubilant Life Sciences is the pharmaceuticals and life sciences arm of the vast Jubilant Bhartia Group, a conglomerate with over 36,000 employees encompassing diverse sectors such as oil, gas, automobiles, aerospace, food, agrochemicals, and polymers. Jubilant entered the drug discovery services business in 2003.[234] With 6100 employees worldwide, of which around 700 in discovery services, the company has developed from a manufacturer of bulk chemicals, incorporated in 1978, into one of the main research and development service providers in India. The company has been engaged in multiple drug discovery collaborations, including Lilly, Amgen, Forest, Orion, Endo, or Johnson & Johnson (J&J), and in 2016, initiated a strategic alliance with Sanofi to discover drugs for metabolic disorders.[235] More recently Jubilant started transforming itself into a dual-business model company, with the creation in 2007 of Jubilant Innovation, the company’s branch for the discovery and development of proprietary or co-owned molecules. The first effort to enter drug development, was by partnering with CGI Pharmaceuticals in 2008 for the development of CGI-1842 (subsequently known as J-101), a tyrosine kinase inhibitor targeting selectively vascular endothelial growth factor receptor type 2 (VEGFR2), ephrin type-B receptor 4 (EphB4) and platelet-derived growth factor receptor β (PDGFRβ), which reached a Phase 1/Phase 2 stage trial in solid tumors in the US in 2012, but has been abandoned since for lack of efficacy (Supporting Information Table 6b, entry 7).[236] Since 2014, the company has been disclosing its proprietary oncology-focused drug discovery projects, on EGFR kinase inhibitors (JIEM-0186),[237] dual lysine-specific histone demethylase (LSD1)-histone deacetylase inhibitors (JI-97),[238,239] and bromodomain and extra-terminal motif (BET) inhibitors (JUBET-050).[240] Jubilant’s BET BRD4 inhibitor program, including lead compound CK-103, has recently been licensed to Checkpoint Therapeutics (2015) (Supporting Information Table 6a, entries 165–167).[241]

Elder Pharmaceuticals, founded 1989, and active in the manufacturing of APIs and the distribution of products for women’s healthcare, wound care and nutraceuticals, filed two patents in 2008 with Poona College of Pharmacy on anti-inflammatory agents,[242] and on thiazolidinone compounds for the treatment of diabetes.[243] The company has had serious financial issues, and is currently facing bankruptcy.[244] No information is available in annual reports on any internal drug discovery or development activities.[32,245]

IPCA Laboratories, a manufacturer of APIs and generic formulations, and market leader in India for antimalarials, entered NCE research by licensing two antimalarial ozonide development compounds from the Indian Central Drug Research Institute. CDRI-97/78 (in-licensed in 2007) is currently undergoing Phase 1 studies, and CDRI-99/411 (in-licensed in 2008) is likely to have been abandoned at the preclinical stage (Supporting Information Table 6b, entries 8–9).[246] The company initiated in-house drug discovery projects in 2009 to develop treatments for pain, ulcers, and malaria and thrombosis, and claimed to have two compounds in their pipeline for thrombosis and ma-
laria in 2012, but no internal compound appears to have passed the research stage so far.\[247,248\]

**Mankind Pharma**, founded in 1995, has become one of the top-five privately held Indian pharmaceutical companies. It currently counts more than 11,000 employees, of which 200 in its R&D Centre in Manesar, established in 2011, focusing on pharmaceutical development and new drug discovery research.\[249\] The company claims to be active in five new drug discovery projects in the areas of diabetes, arthritis and angina, but no information on the research programs has been disclosed, nor has there been any published NCE patent application.

**Alkem Laboratories** was founded in 1973, and until recently a privately held pharmaceutical company.\[250\] Alkem initiated drug discovery efforts in 2012 in the area of infectious diseases.\[251\] A more recent focus has been on the development of cathepsin K inhibitors for the treatment of osteoporosis, with Alkem-43 as a potential candidate compound (Supporting Information Table 6a, entry 168).\[252-254\] Alkem closed its drug discovery efforts in preparation of its successful initial public offering in 2015, and has attempted to license the project.

**Emcure Pharmaceuticals** was incorporated in 1981, and counts among the top-30 Indian pharmaceutical companies with over 9000 employees.\[255\] The R&D team counts 400 scientists, focusing on API development and formulations research. Around 2014, the company started a “New Drug Discovery Research” group, with so far a single published patent application on acid secretion inhibitors.\[256\] No further information is currently available on Emcure’s drug discovery efforts.

Finally, and although not included in our analysis as the Indian subsidiary of a multinational company, it is worth mentioning the contributions, primarily driven by Indian scientists, of what has been considered by some in the country as an “iconic lab”, AstraZeneca India.\[257\] At a time when the R&D centers of other Western companies had left the country, AstraZeneca, formed by the merger of Astra and Zeneca in 1999, chose to build on the existing Astra Research Centre India (ARCI) in Bangalore.\[258\] Established in 1987 as a nonprofit organization to address the problem of infectious diseases in developing countries, the company initially developed diagnostic tools to identify parasitic diseases, soon followed by drug discovery projects in collaboration with Astra Sweden in the field of antimalarial and antimycobacterial agents.\[259\] The merger resulted, in addition to a change in name to AstraZeneca India Pvt. Ltd., in a modified remit with a focus on antituberculosis drug discovery. The Bangalore group successfully delivered its first development compound, AZD5847, a novel oxazolidinone antibiotic, that entered Phase 1 studies in 2009.\[258,260,261\] This was followed in October 2014, through a collaboration with MMV initiated in 2010, by MMV253 (or AZ13721412), a triaminopyrimidine V-type H+·ATPase inhibitor, a novel class of fast-killer and long-acting antimalarials, as preclinical development compound in 2014.\[262,263\] The collaboration with TB Alliance, also initiated in 2010, yielded a third development candidate, TBA-7371, a potent inhibitor of DprE1, currently undergoing preclinical development.\[264,265\] By January 2014 however, AstraZeneca had announced the closure of its Bangalore R&D center, impacting 168 employees in drug discovery and process R&D.\[257\] The company continued the clinical development of AZD5847, which entered Phase 2 studies in 2012, but was abandoned in 2015.\[258\] TB Alliance found a partner in Lilly for the further preclinical development of TBA-7371, and MMV recovered the rights to MMV253, which was partnered with another Indian company, Zyodus Cadila.\[266\]

### 3.3. From contract research to proprietary discovery projects

India became a hub for drug discovery collaborations in the late-1990s when global pharmaceutical and biotechnology companies started outsourcing non-IP-sensitive chemistry such as chemical libraries, intermediates and reference compounds. Cost arbitrage, together with the availability of synthetic chemistry expertise, and existing knowhow from the generics development and manufacturing business, had largely been the drivers initially, and still are, to a large extent, even though Western companies are looking increasingly for added value beyond cheap labor. The service offerings expanded beyond chemistry into biology and pharmacology, and a number of deals gradually evolved into IP-generating collaborations with Indian inventors, and often into collaborative, integrated drug discovery alliances, with, in selected cases, the elements of risk and reward sharing.

In addition to a growing network of smaller companies, this led to the rise of several large contract research companies. Those that did not initiate proprietary in-house projects are not included in our analysis, although some of the largest deserve being mentioned for their contributions in support of global drug discovery projects.\[23\] **Syngene International Ltd.**, founded in 1994, is the contract research subsidiary of Biocon, and has engaged in collaborations with a number of pharmaceutical and biotechnology companies, of which by far the largest, with over 550 scientists, has been signed in 2007 with Bristol-Myers Squibb (BMS), covering a broad range of integrated drug discovery and development services.\[253,267\] This was followed by Abbott Nutrition (2010), Baxter (2014), and recently by Amgen (2016), all with dedicated centers.\[256\] **TGC Lifesciences (TCGLS)** was established as Chembiotek Research in 1998 and started offering chemistry services from its facilities in Kolkata in 2001, then expanded into multiple service areas, including biology, pharmacology, DMPK, clinical services and bioinformatics.\[269\] Pfizer chose the company at the end of 2009 as a partner for integrated drug discovery services after its acquisition of Wyeth, and terminated the acquired company’s existing large-scale alliance with GVK Bio which had been in place since 2006.\[261,270\]**Sai Life Sciences** was established in 1999, and steadily expanded its chemistry capabilities in drug discovery, process R&D, and manufacturing, and more recently included biology and DMPK.\[271\] Since 2009, the company has been involved in a discovery chemistry collaboration with UCB.\[272\] A more limited number of CROs took the risk of adopting a dual business model, by initiating proprietary projects in addition to external discovery services (Table 2).

**Advinus Therapeutics**, backed financially by the Tata Group, was established in 2005 by the former heads of research and
drug discovery, respectively, at Ranbaxy, who had held previous scientific positions at Bristol-Myers Squibb.\cite{273} The company was launched with a dual business model, having pharmaceutical and agrochemical development services in Bangalore, and a drug discovery research center in Pune, focusing on metabolic, inflammatory, and neglected diseases. Advinus runs both proprietary drug discovery projects with the aim to out-license preclinical drug candidates, and collaborative discovery and development projects. The company entered into collaborations with major companies including MSD, Novartis, J&J, Celgene and Takeda.\cite{274} Advinus has been working on a pipeline of proprietary drug discovery projects, with its most advanced compound, GKM-001, a glucokinase activator having successfully completed a 14-day Phase 2 proof-of-concept study.\cite{275–277} and backup compound GKM-002 at the preclinical level.\cite{278,279} So far, the company has been unable to find a partner for a further development of these compounds. A range of preclinical compounds, initially developed for various indications such as COPD, IBD, Parkinson’s Disease, or inflammatory and autoimmune disorders,\cite{280} have been repositioned more recently for immuno-oncology, including adenosine A2a and A2b receptor antagonists;\cite{281,282} Janus kinase and BTK inhibitors (Supporting Information Table 2a, entries 169–177);\cite{279,277,283–286} However, after the departure of Advinus’ managing director in May 2016,\cite{287} a shift of the company’s emphasis more toward discovery services, followed by a restructuring of its operations, the future of these compounds has become uncertain.\cite{288}

Anthem Biosciences, incorporated in 2006 and headquartered in Bangalore, is a biotech company offering drug discovery and development, as well as process research and manufacturing services.\cite{289} Although the company does not work on proprietary drug discovery projects, it owns intellectual property rights to novel HDAC inhibitors for cancer therapy from an earlier collaboration with Portsmouth Technologies, a virtual drug discovery company,\cite{290} and has plans to partner candidate compounds PAT-1102 33, and PAT-1118 for preclinical development (Supporting Information Table 2a, entries 178–179).\cite{289,291}

Aurigene Discovery Technologies was established 2002 in Bangalore as a subsidiary of Dr. Reddy’s Laboratories, to provide services in medicinal chemistry, structural biology and structure-based drug design.\cite{292} The company rapidly evolved away from pure functional services toward integrated, collaborative, risk-sharing drug discovery alliances, and grew in size, including in 2009 with the absorption of a development group in Hyderabad after Dr. Reddy’s termination of all in-house R&D projects. With over 500 scientists, Aurigene’s current therapeutic focus lies in immuno-oncology, epigenetics, precision oncology and selected targets for inflammatory disorders. Aurigene has entered into a large number of collaborations, including with Novartis, Merck KGaA, Debiopharm, Endo Therapeutics, and Asana Biosciences, which all successfully delivered development candidates.\cite{293} The company initiated proprietary in-house drug discovery projects in 2010,\cite{294} using both small-molecule and peptidic or peptidomimetic approaches, and announced its first licensing agreement with Debiopharm on Debio-1142, an inhibitor of an undisclosed oncology pathway (2011) (Supporting Information Table 6a, entries 180–191).\cite{295} Aurigene has developed a range of inhibitors which block the signaling pathway of PD-1, or Programmed cell death 1, an immunoreceptor which plays an important role in negatively regulating immune responses. Sequences of the extracellular domain of PD-1 that are critical for ligand–receptor interaction, served as starting points for the investigation of 7- to 30-mer peptides derived from human and murine PD-1 sequences, leading to the discovery of the 29-mer AUNP-12/W016A, licensed to Pierre Fabre Médicaments (2014, but returned at the end of 2015).\cite{296,297} Aurigene has also identified shorter peptides and small-molecule peptidomimetics, licensed to Curis, including CA-170/AIDS-170, a dual PD-L1/V-domain Ig suppressor of T-cell activation (VISTA) inhibitor, which entered Phase 1 mid-2016, and CA-327/AUPM-327, a dual PD-L1/T-cell immunoglobulin and mucin-domain-containing molecule-3 (TIM-3) inhibitor, currently at a preclinical development stage. In addition, the agreement with Curis includes CA-4948/AU-4948, an orally active interleukin-1 receptor-associated kinase 4 (IRAK-4) inhibitor for precision oncology.\cite{298–300} Aurigene is also targeting epigenetic regulation mechanisms, for example with pan-BET inhibitors (BRD4/ BRD2/BRD3), such as ODM-207, a quinolin-2(1H)-one derivative which it licensed to Orion, and for which IND enabling studies are currently being pursued.\cite{301–303} Additionally, the companies are also exploring selective BET inhibitors. Other projects continue internally with a strong focus on oncology, including with nicotinamide phosphoribosyltransferase (NAMPT) inhibitors such as AU-4869,\cite{304} covalent K-Ras inhibitors,\cite{305} or CDK7 inhibitors,\cite{306} and RAR-related orphan receptor gamma (ROr) inverse agonists for the treatment of inflammatory disorders.\cite{307} Additional approaches targeted the treatment of infections with PD-1 inhibitors,\cite{293} or with Fabl (enoyl-acyl carrier protein (ACP) reductase) inhibitors such as AEA16 34.\cite{308}

GVK Biosciences, set up in 2001, has become one of the largest contract research organizations and has been engaged in major drug discovery service collaborations with companies such as Wyeth, Endo, or Medivir.\cite{309} In 2013, GVK Bio formed a joint venture with Onconova for lead optimization and subsequent development for IND filing on two early research compounds,\cite{309} including GBO-006-1 (previously ON-1231320), a PLK2 inhibitor for the treatment of breast cancer, which appears to have been discontinued. Around 2014, GVK Bio initiated internal projects, with the aim to license these at an early stage to potential clients. As a first example, GVK-TrkA, a selective tropomyosin receptor kinase A (TrkA) inhibitor for the treatment of cancer, progressed into preclinical development (Supporting Information Table 6a, entry 192).\cite{310,311} A second project with GVKO1406, a compound targeting PI3Kβ inhibition, reached the lead optimization stage.\cite{312}

3.4. The rise of drug discovery at biotechnology companies

The launch of startups and small biotechnology companies with the aim to generate IP and licensing revenues by discovering new drugs and by partnering these for development, is a more recent addition to the country’s pharmaceutical envi-
Kareus Therapeutics was established in 2007 by former members of Dr. Reddy’s Laboratories, and runs currently as a virtual company headquartered in Switzerland. The company’s activities focus on CNS diseases, diabetes and chronic pain. Kareus currently has two compounds in development in the US, namely KU-046, in Phase 1 studies for the treatment of Alzheimer’s disease, exploring further options for multiple sclerosis and fragile X syndrome, claimed to be acting by dual targeting of oxidative stress and energy deficiency by linking niacin derivatives and redox-active aromatic compounds, and KU-5039 for diabetes, likely to be a fatty acid analogue activator of AMPK (Supporting Information Table 6a, entries 193–194).

Connexios Life Sciences was established in 2003, backed financially by the venture investing arm of a co-founder of Infosys, one of India’s largest IT service companies. The company focused initially on developing systems biology approaches, databases and cell-based assays, but in 2008, took the strategic decision to launch full-scale drug discovery operations, specialising in metabolic diseases such as type 2 diabetes. Connexios’ most advanced compounds are CNX-012-570, an AMPK activator for the treatment of type 2 diabetes, recently licensed to Boehringer Ingelheim, CNX-011-67, a GPR40 agonist, for which the company has been looking for development partners since 2012; CNX-013-B2, an activator of retinoid X receptor (RXR) (Supporting Information Table 6a, entries 205–206). Connexios is a virtual company headquartered in Switzerland.

Rhizen Pharmaceuticals S.A. was incorporated in Switzerland, with the aim to develop and partner compounds originating from Incozen, a biotech company founded in 2008 in Hyderabad to discover novel treatments for oncology and inflammation (Supporting Information Table 6a, entries 199–204). Both companies were established with funding from Alembic Ltd. (see above). In 2012 RP-5264 (now TGR-1202) 35, a selective PI3Kδ inhibitor for the treatment of hematological lymphomas, was licensed to TG Therapeutics, and has recently entered Phase 3 studies as a combination treatment together with TGR-1101, an anti-CD20 monoclonal antibody (mAb) for chronic lymphocytic leukemia. Phase 2 studies with TGR-1202 were still ongoing as a stand-alone treatment in 2016. Recently RP-6530, or tenalisib, a dual PI3K/δ inhibitor for the treatment of hematological malignancies, entered Phase 1 studies. Further compounds reached different stages of preclinical evaluation, including RP-1400, a c-Met kinase inhibitor, abandoned in 2015, and RP-3128, a CRAC inhibitor. RP-6503, an inhaled dual PI3K/δ inhibitor, was licensed to Novartis at the end of 2015 for the treatment of airway diseases, and is potentially structurally related to a recently patented single enantiomer. In 2016 Rhizen disclosed PR10107, a glutaminase inhibitor for the treatment of cancer. In addition, the company is developing RV1001, a PI3Kδ inhibitor for veterinarian use in canine lymphoma (Phase 2).

Sphaera Pharma was launched in 2008, with laboratory space in Manesar, Haryana, and headquarters in Singapore. The company filed a first patent in 2011 on PI3K/mTOR inhibitors, of which one, SPR965, has reached the preclinical evaluation stage. The compound is likely to be structurally related, if not identical to a compound recently described in a publication. In 2015, Sphaera announced a collaboration with the International Centre for Genetic Engineering and Biotechnology (ICGEB), funded by the Wellcome Trust for the development of inhibitors of niacin receptor 1 (NIACR1), also known as GPR109A, to treat multidrug-resistant infections, that led to SPR113 which entered preclinical development (Supporting Information Table 6a, entries 205–206).

Curadev was founded in 2010 in Noida, and currently employs around 50 people. The company has integrated drug discovery activities, offering services in parallel working on proprietary projects. In 2010, Curadev entered into a research collaboration with Endo Pharmaceuticals for cancer up to candidate selection stage, and in 2011, a collaboration with Medivation. Curadev’s most advanced internal program on dual indoleamine 2,3-dioxygenase (IDO)/tryptophan-2,3-dioxygenase (TDO) inhibitors, originating from its Endo partnership, is at the preclinical development stage. Its lead compound CRD1152 (now RG70099) has been licensed to Hoffmann-La Roche in April 2015 (Supporting Information Table 6a, entry 207).

Shantani Proteome Analytics, founded in 2010 in Pune, offers chemical proteomics services in target identification, toxicity profiling, or drug repurposing. More recently the company entered the field of drug discovery with a proprietary project to treat type 2 diabetes, and a first-in class lead compound at the preclinical stage. This is likely related to a recently published patent application by Shantani on indazole compounds including NDS100179 37, together with the Council of Scientific and Industrial Research (CSIR) and the National Chemical Laboratory (Supporting Information Table 6a, entry 208).

Vyome Biosciences was founded in 2010, and currently consists of a team of around 30 scientists. The company focuses on dual-action compounds joining two known antibiotics by a chemical linker, and on conjugate-based antifungal and antibacterial products, by derivatising existing drugs with a hydrolytically or enzymatically labile linker and a carrier, including fatty acids, surfactants or polymers to formulate the drug into nanoparticles. V8-1953, a dual-acting compound likely to combine a nitro-imidazole antibiotic and a fluoroquinolone joined with a linker moiety, is Vyome’s first NCE to be approved by the FDA for Phase 1 studies (Supporting Information Table 6a, entries 209–210). A second, unnamed compound recently entered preclinical studies.

Vitas Pharma is a small startup drug discovery company founded in 2011, based in the Technology Business Incubator.
at the University of Hyderabad, with currently about 10 people. The company focuses on developing treatments for infectious diseases, particularly, drug-resistant nosocomial infections. The most advanced compound, presumably VT-02-00068 38 or an analogue thereof,356 prevents fatty acid biosynthesis, a vital metabolic pathway in bacteria, by inhibiting the enzyme FabI, and is currently undergoing safety and toxicity testing (Supporting Information Table 6a, entry 211).359 It is equally potent against diverse MRSA strains.

Invictus Oncology, incorporated in 2011 and based in New Delhi, develops nanotherapeutics for cancer treatment.360 Invictus has licensed the rights to a technology developed at Harvard Medical School, consisting in decreasing the toxicity of platinum-based anticancer drugs by conjugating them to cholesterol, and assembling them into nanoparticles.361 As tested on cisplatin, the increased nanoparticle size allows the drug to enter cancer cells, which have wide pores on their surface, but not normal cells, with reduced pore sizes. The company is also applying the technology to its own new platinum drugs as well as antibody drug conjugates. IO-125 39, the company’s lead compound, is undergoing preclinical development studies (Supporting Information Table 6a, entry 212).362,363

Krish Biotech was established in 2009 near Kolkata to offer preclinical services including analytical and toxicological testing.364 In 2015, the company initiated drug discovery efforts, led by former Piramal scientists, in the areas of metabolic disorders, oncology, immunology, pain and inflammation. With the aim of building a proprietary research pipeline, including through the acquisition of external compounds, Krish Biotech in-licensed two preclinical stage compounds from Piramal: KBR1001 (or KBGPL1001), a RORγt antagonist for the treatment of autoimmune and inflammatory disorders,365 and KBR2001 or (KBGPL2001), a GPR120 agonist for diabetes and metabolic disorders.366 Three additional projects targeting oncology and pain are currently at the discovery stage (Supporting Information Table 6a, entries 213–214).367

4. Results and Discussion

4.1. Proprietary drug discovery at Indian companies

Our analysis identified 28 major Indian pharmaceutical companies and 14 biotech and startup companies that have reported proprietary NCE R&D with preclinical or clinical development compounds between 1994 and mid-2016 (Tables 1 and 2).

Among top-100 pharma companies, overall R&D size and productivity vary considerably, however, and only 12 companies have engaged in long-term and large scale drug discovery efforts, and have produced a significant number of development compounds (Supporting Information, Tables 6–8). For the majority, drug discovery remained a rather limited activity, as illustrated for example, by isolated patenting of internal research results, or by academic collaborations.

Few CROs have ventured successfully into proprietary research. Advinus had been a pioneer in this field since its inception in 2005, although the failure to license out a single of its internal compounds has recently led to a refocus of the company’s activities, and it remains to be seen if the current discovery pipeline survives. Aurigene is currently leading the way, with a strong proprietary portfolio and four out-licensed compounds, and two more under an option agreement. The number of biotech companies and startups with proprietary development compounds remains small with 10 companies.

Since the initiation of drug discovery by Dr. Reddy’s Laboratories in 1994, Indian companies have disclosed a total of 214 proprietary preclinical and clinical stage development compounds, of which 168 originated from large pharma companies, and 46 from contract research and biotech companies. Of these, 83 compounds were progressing in the pipeline by mid-2016 according to publicly available information (Figures 2 and 3, Supporting Information Tables 8a and 8b). Given the inherent fluctuations of R&D pipelines, this number is likely to evolve as more information becomes available on existing pipelines (e.g., Advinus, Connexios), and as additional development compounds will be disclosed.

Despite this significant number of compounds, Zydus Cadila’s saroglitazar, launched in 2013, remains so far the only compound that was entirely discovered and developed by an Indian company. Three more compounds reached the level of Phase 3 studies: Dr. Reddy’s ragaglitazar and balaglitazone, both discontinued, and more recently, Rhizen’s RP5264/TGR-1202, in combination with an anti-CD20 mAb, licensed to TG Therapeutics. Phase 2 stage compounds peaked in 2012 with 15 compounds, but this figure has decreased slightly since. The number of Phase 1 compounds has been quite stable with about 20 compounds each year since 2009, but with a notable recent increase in compounds from biotechnology companies (from 2% of the total pipeline in 2009 to 31% in 2016). Preclinical stage compounds have more than doubled since 2009, again driven largely by biotech companies (from 4% in 2008 to 71% in 2016).

At the major pharmaceutical companies, many internal R&D efforts have not been met with the expected success, as seen from those companies that have abandoned drug discovery in the meantime, be it after being acquired (Dabur, Matrix, Ranbaxy), before going public (Alkem), or after failing to deliver commercial compounds despite significant investments (Dr. Reddy’s, Piramal). Other companies have significantly reduced the number of NCEs in their pipeline, including Zydus Cadila (from 13 in 2011 to 5 in 2016), Glenmark (from 8 in 2006 to 2 in 2016), and Sun (from 5 in 2012 to 3 in 2016). One significant exception to this is Lupin Pharma, which restructured completely its R&D organization in 2010 and launched a range of new NCE projects, with currently 4 compounds undergoing clinical development. As an overall result, however, the combined pipeline contribution by major companies has fallen from a peak in 2011 with 58 compounds (89% of total pipeline), to 41 compounds (or 49% of total pipeline) in 2016.

Biotec technology and startup companies, in contrast, have grown in number, size and research output, as illustrated by an increasing number of early development stage compounds, led currently by Aurigene. Several of the more recently founded companies have also been successful in generating preclinical compounds that attracted global partners, such as Rhizen.
| Entry | Company | Year drug discovery initiated | Year company established | Rank \(^a\) | Estimated drug discovery or R&D headcount (year) | Total pipeline compounds \(^b\) | Status 2016 |
|-------|---------|------------------------------|--------------------------|-----------|-----------------------------------------------|---------------------------|-------------|
| 1     | Dr. Reddy’s Laboratories | 1994 | 1984 | 2 | 320 in NCE R&D (2005) | 27 | Exited drug discovery in 2009 |
| 2     | Ranbaxy (now part of Sun Pharma) | 1995 | 1961 | \((-\))\(^c\) | 280 in “New Drug Discovery Research”; 1400 in R&D (2008) | 16 | Exited drug discovery in 2008 after acquisition by Daiichi-Sankyo |
| 3     | Torrent Pharmaceuticals | 1997 | 1972 | 9 | 130 in NCE discovery research (2008–14) | 6 | Active NCE R&D, three compounds in pipeline |
| 4     | Wockhardt Ltd. | 1997 | 1967 | 13 | 850 in R&D (2015) | 15 | Active NCE R&D, five compounds in pipeline |
| 5     | Piramal Life Sciences | 1998 | 1988 | 17 | 360 in NCE R&D (2011) | 16 | Exited drug discovery in 2014 |
| 6     | Dabur Research Foundation (now Fresenius-Kabi Oncology) | 1998 | 1886 | \((-\))\(^c\) | 20 in oncology drug discovery (2001) | 0 | Exited drug discovery in 2010 after acquisition by Fresenius-Kabi |
| 7     | Sun Pharma | 1999 | 1993 | 1 | 275 at SPARC R&D (2015) | 8 | Active NCE R&D, three compounds in pipeline |
| 8     | Alembic Ltd. | 1999 | 1907 | 20 | NA | 0 | Collaboration with NCL (1999-2003); investment in Incozen Therapeutics and Rhizen Pharmaceuticals (2008) |
| 9     | Zydus Cadila (Cadila Healthcare) | 2000 | 1995 | 6 | 250 in NCE R&D (2016) | 15 | Active NCE R&D, one compound launched (2013), four compounds in pipeline |
| 10    | Cadila Pharmaceuticals | 2000 | 1995 | 34 | NA | 0 | Develops mainly combination preparations; drug discovery collaboration with IIM |
| 11    | FDC Ltd. | 2000 | 1940 | 42 | NA | 1 | Patent filings (2002–13) with National Chemical Laboratory (Pune), no internal drug discovery |
| 12    | JB Chemicals & Pharmaceuticals | 2000 | 1976 | 37 | NA | 1 | Exited drug discovery in 2006 |
| 13    | Cipla | 2000 | 1935 | 5 | NA | 0 | Patent filings (2000–01) with University of Mumbai, no internal drug discovery |
| 14    | Glenmark Pharmaceuticals | 2001 | 1977 | 8 | 300 NCE R&D (2015) | 19 | Active NCE R&D, four compounds licensed (all failed), one under option agreement (ongoing), one additional compound in pipeline |
| 15    | Lupin Ltd. | 2001 | 1972 | 3 | \(-\)\(^c\) | 7 | Active NCE R&D, four compounds in pipeline |
| 16    | Reliance Life Sciences | 2001 | 2001 | 58 | NA | 2 | Exited NCE R&D in 2010 |
| 17    | Orchid Pharma | 2002 | 1992 | 47 | 130 in drug discovery (2013) | 5 | Halted drug discovery in 2014; one compound licensed to Allecr (2013), development ongoing |
| 18    | Suven Life Sciences | 2003 | 1989 | 59 | 120 in NCE R&D, out of 386 in R&D (2016) | 15 | Active NCE R&D, eleven compounds in pipeline |
| 19    | Natco Pharma | 2004 | 1981 | 38 | 15 in oncology drug discovery (2014) | 3 | Active NCE R&D, two compounds in pipeline |
| 20    | Panacea Biotech | 2005 | 1984 | 51 | 110 in drug discovery (2013) | 4 | Halted internal drug discovery in 2014; two compounds in pipeline |
| 21    | Matrix Laboratories (now Mylan) | 2005 | 2000 | \((-\))\(^c\) | 18 in drug discovery (2006) | 2 | Exited drug discovery after acquisition by Mylan (2006) |
| 22    | Hetero Drugs | 2006 | 1993 | 7 | NA | 2 | NCE drug discovery mainly targeting HIV, also HCV, diabetes and cancer |
| 23    | Jubilant Life Sciences | 2007 | 1978 | 11 | NA | 3 | Active NCE R&D, three compounds in pipeline (one licensed in 2016) |
| 24    | Elder Pharmaceuticals | 2008 | 1989 | 44 | NA | 0 | Patents filed with Poona College of Pharmacy (2008), no internal drug discovery |
| 25    | IPCA Laboratories | 2009 | 1949 | 22 | NA | 0 | Claimed two compounds in pipeline (2012), but no development reported |
| 26    | Mankind Pharma | 2011 | 1995 | 15 | NA | 0 | No published NCE patent applications |
| 27    | Alkem Laboratories | 2013 | 1973 | 12 | 20 in drug discovery (2014) | 1 | Exited drug discovery prior to going public in 2015 |
| 28    | Emcure | 2014 | 1981 | 26 | NA | 0 | One published NCE patent application |

| Total: | 168 |

\(^a\) Ranking by 2016 revenue or latest available figure (Supporting Information Table 5). \(^b\) Status mid-2016. \(^c\) Ranked #1 in acquisition year 2008. \(^d\) Ranked #37 in acquisition year 2008. \(^e\) Ranked among top-10 in acquisition year 2006.
Table 2. Proprietary drug discovery activities at Indian biotech companies.

| Entry | Company | Year[a] | Development compounds | Estimated headcount | Status 2016 |
|-------|---------|---------|-----------------------|---------------------|-------------|
| **a) Contract research companies with proprietary projects** | | | | | |
| 1 | Advinus | 2005 | 9 | NA | NCE R&D in multiple therapeutic areas, one compound in Phase 2, recent emphasis on drug discovery services |
| 2 | Anthem Biosciences | 2009[b] | 2 | NA | No ongoing internal drug discovery, isolated IP |
| 3 | Aurigene | 2010[c] | 12 | NA | NCE R&D with a strong focus on oncology, four compounds out-licensed and two under option agreement |
| 4 | GVK Bio | 2014[d] | 1 | NA | Limited proprietary drug discovery activity |
| **b) Biotech companies** | | | | | |
| 5 | Kareus Therapeutics | 2007 | 2 | > 10 | NCE R&D to treat CNS diseases and diabetes |
| 6 | Connexios Life Sciences | 2008[e] | 4 | 180th | NCE R&D focusing on metabolic diseases, one compound out-licensed, currently focus on development activities |
| 7 | Rhizen Pharmaceuticals/Incozen Therapeutics | 2008 | 6 | 40th | NCE R&D for oncology and inflammation, two compounds out-licensed, one undergoing Phase 3 studies |
| 8 | Sphaera Pharma | 2008 | 2 | NA | NCE R&D in oncology and infectious diseases |
| 9 | Curadev | 2010 | 1 | 50th | NCE R&D in oncology, one compound out-licensed |
| 10 | Shantani Proteome Analytics | 2010 | 1 | < 10 | Limited proprietary drug discovery activity |
| 11 | Vyome Biosciences | 2010 | 2 | 30th | NCE R&D based on cleavable linker and nanoparticle technologies to treat infections |
| 12 | Vitas Pharma | 2011 | 1 | 10th | NCE R&D to treat drug-resistant nosocomial infections |
| 13 | Invictus Oncology | 2011 | 1 | 30th | Platinum-based nanotherapeutics to treat cancer |
| 14 | Krish Biotech | 2015[f] | 2 | NA | NCE R&D in multiple therapeutic areas, two compounds in-licensed from Piramal |

Total: 46

[a] Year company established unless specified otherwise. [b] Year proprietary patent filed. [c] Year proprietary drug discovery initiated. [d] Figure for year 2014. [e] Estimated combined headcount Rhizen/Incozen (2014).

Figure 2. Development compounds at Indian pharmaceutical and biotechnology companies.
Pharmaceuticals, Connexios, and Curadev. The increase in development compounds coming out of India is thus currently entirely driven by R&D focused biotech companies, which for the first time surpassed pharma companies with 42 compounds in 2016, growing from 2% of the overall pipeline in 2009 to 51% in 2016.

Whereas some of the major Indian pharmaceutical companies have the ambition to develop and market their own drugs, high costs and long timelines, combined with the lack of experience in clinical development lead most, and in particular smaller biotech companies, to prefer out-licensing deals to finance part or all of their development costs. This is illustrated by the fact that 23 small-molecule compounds have been licensed to global pharmaceutical companies or have been under option agreements over the past two decades (Table 3).

Initially dominated by major pharma companies, in particular DRL, Ranbaxy and Glenmark, the out-licensing model experienced several resounding failures, including in Phase 2 studies, which led some analysts to claim the death of the Indian out-licensing model. Whereas the steady decrease of licensed compounds appears to confirm this for large Indian pharma companies, the reverse is true for biotech companies with 10 licensing or option agreements since 2011, largely led by Aurogene, and illustrates the continuing attractiveness of Indian development compounds for global companies.

4.2. Development compounds by indication and target class

Counting all, including multiple indications targeted by these development compounds, endocrinology and metabolic disorders, together with oncology dominate the therapeutic areas, representing almost half of all indications covered by drug discovery projects in India, followed by infections, immunological and rheumatological diseases, neurology and pulmonary and respiratory diseases. All remaining disease areas combined represent less than 10% (Figure 4, Supporting Information Table 8c). This distribution is clearly quite different from the
Table 3. Licensing and option agreements.

| Company                  | Compound          | Mode of action/therapeutic area                                      | Status mid-2016 (highest phase reached) |
|--------------------------|-------------------|---------------------------------------------------------------------|-----------------------------------------|
| Dr. Reddy's Laboratories | balaglitazone (DRF-2593), 1 | PPARγ agonism/diabetes                                                | Licensed to Novo Nordisk (1997–2004); Rheosciences (2005–2010); DRL owns development in 2010, Phase 3—stop 2011 |
|                          | ragaglitazar (DRF-2725), 2 | Dual PPARγ/γ agonism/diabetes                                          | Licensed to Novo Nordisk (1998–2002), Phase 3—stop 2002 |
|                          | DRF-4158 (LBL-752)  | Dual PPARγ/γ agonism, HMG-CoA reductase inhibition/metabolic disorders | Licensed to Novartis (2001), Preclinical—stop 2003 |
| Ranbaxy                  | RBx-2258 (SPM-969), parvocin, pamrinasin, 4 | α1/β-Adrenoceptor antagonism/benign prostatic hyperplasia             | Licensed to Schwarz Pharma (2002), Phase 2—stop 2004 |
|                          | RBx-10558, PPD-10558, 5 | HMG-CoA synthase inhibition/hypercholesterolemia                       | Licensed to Furler Pharma/PPD (2007); Phase 2—stop 2011 |
| Torrent                  | TRC-4186, 8        | AGE breaker/diabetes-related cardiovascular disorders                 | Option agreement with Novartis (2002–2005); Phase 2 completed 2015 |
| Glenmark                 | GRC-3886 (oglemilast), 23 | PDE-4 inhibition/asthma, COPD                                        | Licensed to Forest (2004), Teijin (2005), Phase 2—stop 2009 |
|                          | GRC-6211, 25       | TRPV1 antagonism/pain, incontinence, asthma                           | Licensed to Lilly (2007), Phase 2—stop 2008 |
|                          | GRC-8200 (melogliptin), 24 | DPP-IV inhibition/diabetes                                           | Licensed to Merck KGaA (2006), returned 2008, Phase 2—stop 2011 |
|                          | GRC-15300 (SAR292833) | TRPV3 antagonism/pain                                                | Licensed to Sanofi (2010), Phase 2—stop 2014 |
|                          | GRC-27864          | mPGES-1 inhibition/inflammation, pain                               | Option agreement with Forest Labs (2012), Phase 1—ongoing |
| Orchid                   | OCID-5090/AAl101, 30 | Jα-lactamase inhibition/bacterial infections                          | Licensed to Allecr Therapeutics (2013), Phase 1, France—ongoing |
| Jubilant                 | CK-103 (UBET-050)  | BET BRD4 bromodomain inhibition/cancer                               | Licensed to Checkpoint Therapeutics (2016), preclinical—ongoing |
| Aurigene                 | Debio-1142         | Kinase inhibition/cancer                                              | Licensed to Debiopharm (2011), preclinical—stop 2014 |
|                          | AUNP-012 (W014A)   | PD-1 inhibition/cancer                                               | Licensed to Pierre Fabre (2014)—preclinical stop 2015 |
|                          | ODM-207            | BET bromodomain inhibition/cancer                                    | Option agreement with Orion Pharma (2014), preclinical—ongoing |
|                          | CA-170 (AUPM-170)  | Dual PD-L1/Vista inhibition/cancer                                    | Licensed to Curis (2015)—preclinical ongoing |
|                          | CA-327 (AUMP-327)  | Dual PD-L1/Tim-3/cancer                                              | Option agreement with Curis (2015), preclinical—ongoing |
|                          | CA-4948 (AU-4948)  | IRAK-4 inhibition/cancer                                             | Licensed to Curis (2015), preclinical—ongoing |
| Connexios                | CNX-012-570        | AMPK activation/diabetes                                             | Licensed to Boehringer Ingelheim (2014), preclinical—ongoing |
| Rhizen                   | TGR-1202 (RPS264), 35 | Selective PI3Kγ kinase inhibition/cancer                             | Licensed to TG Therapeutics (2012), Phase 2/3—ongoing |
|                          | RP-6503            | Dual PKδ/γ/δ kinase inhibition/asthma, COPD                          | Licensed to Novartis (2015), preclinical—ongoing |
| Curadev                  | RG70999 (CRD1152)  | Dual IDO/TDO inhibition/cancer                                        | Licensed to Roche (2015), preclinical—ongoing |

The burden of diseases in India itself, where the leading causes are maternal and neonatal conditions, followed by cardiovascular diseases and diabetes, various infectious diseases, neuropsychiatric conditions, respiratory diseases and cancer, and corresponds more to the needs resulting from the leading Western diseases, that is, diabetes and cardiovascular disorders, cancer and neuropsychiatric conditions.[364]

With the exception of startups, few Indian companies have specialized entirely in particular disease areas, such as Wockhardt in anti-infectives, Suven in CNS diseases, Natco and Jubilant in oncology, or at least partially, such as Zydis Cadila in metabolic disorders, or Aurigene with a strong focus on oncology. The majority of Indian companies have opted to spread their efforts over multiple therapeutic areas (Figure 5, Supporting Information Table 8e). Few companies have focused on specific targets, such as Suven on 5-HT6 receptors, or Wockhardt on fluoroquinoline and oxazolidine type antibiotics, and some others have a bias toward certain target classes, such as Aurigene and its kinase platform, but in general companies adopted a broad approach with multiple target types.

4.3. Novelty of projects

Of all new FDA-approved NCEs between 1999 and 2013, almost one third are first-in-class compounds, as modulators of an until then unprecedented target or biological pathway,[369] and the share of potentially first-in-class drugs in the current global pipeline has been estimated to be on average 70%.[370] India’s past and current discovery pipeline is far from reaching 23 classes, that is, GPCRs, kinases, and nuclear signaling pathways, represent about half of all targets (46%) (Figure 6, Supporting Information Table 8e). Few companies have focused on specific targets, such as Suven on 5-HT6 receptors, or Wockhardt on fluoroquinoline and oxazolidine type antibiotics, and some others have a bias toward certain target classes, such as Aurigene and its kinase platform, but in general companies adopted a broad approach with multiple target types.
comparable figures, as the vast majority of modes of action have been extensively targeted previously by other companies, such as PDE4 inhibitors, DPP-IV inhibitors, kinase inhibitors, or oxazolidinone and fluoroquinolinone antibiotics. Lack of novelty, or lack of differentiation from existing development compounds, are therefore likely to be key factors that prevented in a number of cases Indian companies from finding global development partners.

However, this does not mean that Indian companies are not innovating in drug discovery. Even though Zydus Cadila’s saroglitazar has only been one of many glitazars that entered development, it has been the first one to reach the market in 2013. Fifteen years earlier, Dr. Reddy’s had been among the first companies to work on glitazars, with ragaglitazar reaching Phase 3 trials before being abandoned. Glenmark’s GRC-15300 had been the first TRPV3 inhibitor to enter clinical trials, and the company’s GRC-17536 has the potential to become a first-in-class TRPA1 inhibitor for the treatment of pain. Advinus’ glucokinase activator, although only one out of more than 20 compounds that have entered clinical trials, is an orally available, potential first-in-class drug with the advantage over earlier, discontinued development compounds of being liver-selective with a lower hypoglycemia risk. Sun’s Bcr-Abl tyrosine kinase inhibitors SUN-K706 and follow-on compound SUN-K954 are active against native Bcr-Abl as well as Abl T315I mutations, the most resistant form of mutation in leukemic cells, and are more selective with respect to a range of other kinases inhibited by ponatinib, the currently used benchmark inhibitor, which might contribute to that compound’s toxicity profile which limits its clinical use. Whereas several of Aurigene’s programs aim at developing best-in-class compounds with significant improvements over competitors (for example, its inhibitors of BET, NAMPT, or Fabl), the company’s PD-1 inhibitors licensed to Curis are the first highly potent and orally available small-molecule compounds targeting Programmed cell death-1. CA-170, which has recently been nominated as development candidate, is a first-in-class dual-acting molecule targeting both Programmed cell death ligand-1 (PD-L1) and V-domain immunoglobulin suppressor of T-cell activation (VISTA). Jubilant’s JIEM-0186 is specifically targeting non-small cell lung cancer associated with EGFR mutants L858R or T790M, and shows a high selectivity against cells carrying the wild-type EGFR. Among the smaller companies, Curadev is targeting a highly competitive area with its potentially first-in-class dual IDO and TDO inhibitors, and Shantani, based on the use of its proteomics platform, has reported an early development compound with a novel mechanism of action for the treatment of type 2 diabetes.

Figure 4. Development compounds by indication.
4.4. Success rates and timelines

Success rates and time spent by development phase have been widely used as parameters to quantify efficiency in pharmaceutical R&D. Current success rates by phase are defined as the number of development compounds that advance to the next phase, divided by the number of compounds that entered the phase from which is subtracted the number of compounds of yet unknown fate, for example, those in ongoing studies.

We have compiled available data (Supporting Information Table 7) on attrition and timelines for the 214 compounds that entered preclinical development, of which 82 progressed to Phase 1, 34 to Phase 2, and 4 to Phase 3, with 1 compound launched. Although the very low number of drug candidates reaching Phase 3, together with the lack of precision in collection timelines do not allow us to generate statistically significant values for all variables, we still believe our analysis to be of relevance, as it illustrates for the first time ever efficiency trends in Indian drug discovery, which allow a comparison with industry figures (Table 4, Supporting Information Table 8).

With the exception of Phase 1 trials, for which the success rate of 54% lies well within the range reported for industry, the chances for successfully transitioning to higher phases are considerably lower at Indian companies than the industry average. The very low success rate of 17.4% during Phase 2 trials could hint at an overall less efficient selection process during earlier phases, and therefore expensive terminations in advanced stages. This is particularly true for the three major companies that abandoned drug discovery (Dr. Reddy’s, Ranbaxy and Piramal), with 9 out of 11 compounds failing in Phase 2, and none completing successfully Phase 3 studies, where 2 out of 2 failed. These lower success rates are compounded by the increased time spent by phase, especially at the earlier stages. Even if the nearly twofold increase in time spent at the preclinical level could be in part the result of capturing with too little precision this first stage of development, clinical phases, too, take considerably longer to complete, and make the drug discovery process at Indian companies considerably less efficient than the industry average. It remains to be seen if the large
number of compounds that have entered development between 2007 and 2016, and of which many are currently progressing at the early stages, will be able to modify this trend significantly. It would also be interesting to compare the Indian success rates to those of other emerging countries, but these are to our knowledge not yet available in the public domain.

4.5. Drug discovery and R&D investments

All major Indian pharmaceutical companies with significant drug discovery and development activities have reported considerable R&D expenditures in their annual reports, usually in the range of 5–10% of revenues. However, it must be pointed out that NCE research is in general only a minor component of this, and that the bigger part goes toward generics development, formulation and drug delivery technologies, or process R&D. This can be assessed from those cases where drug discovery expenditure is specifically mentioned, or can be calculated from available data. Based on these, we estimate that an average of 20–30% of the total R&D budget is dedicated to NCE research and development, even though some analysts estimate that in specific cases as little as 10% goes to new discovery research.

Assuming even an average spending on NCE R&D of 25% of total R&D expenditures, this brings the overall investment in new drug discovery and development down to around 2%, about one tenth of the average spend on R&D by the US pharmaceutical industry, with about 20% of sales.

5. Conclusions and Outlook

Since the initiation of drug discovery by major companies in the 1990s, Indian pharmaceutical R&D efforts have resulted in over 200 preclinical- and clinical-stage development compounds, of which only one has reached the market thus far. This illustrates the tremendous accumulation of R&D capacity and of know-how that has occurred over a time span of two decades, and at the same time its weakness in terms of efficiency. With slightly over 80 active pipeline compounds, India is far from being the drug discovery powerhouse it once had the ambition to become. The fact that several of the large investors in pharmaceutical R&D have closed down their drug discovery units in the meantime, and that others have decreased their pipeline, shows to what extent the industry, which had been familiar with the generics business, had underestimated the challenges that come with innovative NCE discovery and development.

This is likely due to a range of factors. One is a skill gap. The Indian Patent Act of 1970, with its focus on process patents and generics manufacturing, despite the social good it did in India, and arguably worldwide, by making good quality generics affordable to poor countries, removed all incentives to discover new medicines. The consequence was a rapid loss of skills, as Western companies closed their research departments, and as drug discovery-related disciplines, including medicinal chemistry, biology and pharmacology, declined in the Indian science education system. These skills were again built up...
gradually by the pioneer pharma companies, and accelerated
with the rise of contract research companies, as these evolved
from custom synthesis, into higher added value services in-
cluding medicinal chemistry, discovery biology, in vivo pharma-
cology, DMPK, and early toxicity models. This has been
possible at the expense of in-house training, since a recent in-
dustry survey estimated that 66% of the existing manpower is
not industry ready, highlighting the misfit between academic
training and industry needs.

Some of the basic problems that need to be addressed in
order to strengthen weaknesses in the scientific education
system have been summarized in recent reports. A cer-
tain number are due to internal issues, such as inadequate fa-
cilities and quality of teaching, bureaucracy and political influ-
ence. Others are a consequence of the historical deficiency of
interactions between industry and academia or public research
institutions, because existing collaborations are still considered
by a large majority as “limited”, and by only 10% as “good”,
due to the lack of interest for “applied science”, profound dis-
trust, or different priorities and key performance indicators,
such as publications in academia versus patents and commer-
cialization in industry.

All prevent science from being considered as an attractive
career path, with as a consequence a severe brain drain, as
40% of India-born researchers were working overseas in
2011. A series of initiatives have been launched, aiming to
attract experienced returnees, that is, researchers who have
spent part of their scientific career abroad, back into the coun-
try with a range of fellowships in all areas of science and bio-
technology. With an estimated figure of 750 fellowships since
2006, these are, however, likely to be insufficient for the coun-
try’s needs.

The industry itself has also evolved, but needs to progress
further. There has been a gradual shift in contributions to the
growing pipeline away from the established pharmaceutical
companies, whose contribution peaked in 2011, toward small-
er, research-intensive biotechnology companies. These do not
only benefit from the availability of trained scientists with rele-
vant industrial experience in the country, but also tend to
focus on specific disease areas or target classes, which gives
them the opportunity to carve out niches to be successful in
their particular areas of expertise, as illustrated by a number of
recent licensing deals. The industry has started to integrate
the importance of innovation, and is moving away from low-risk
follow-on projects, which certainly decreased the risk, but on
the other hand led to molecules without preclinical and clinical
advantages over existing development compounds, and were
therefore difficult to out-license. Current projects are targeting
increasingly best-in-class compounds that address specific
issues of compounds currently progressing in the global pipe-
line, if not compounds that have the potential to become first-
in-class drugs.

There are, however, other weaknesses that need to be ad-
dressed. Overall investment in R&D, and more specifically in
NCE drug discovery, needs to be increased, as it has been lag-
ning far behind global industry average. More biotechnology
companies need to be created, and funded appropriately. The
US is home to over 40 pharmaceutical companies and an esti-
imated 1700 biotech companies, which dwarfs India’s life sci-
cences landscape. India is, however, making progress in putting
in place an ecosystem which is more conducive to biotechno-
ology entrepreneurship, through a series of grant schemes to
foster innovation, and bio-incubators which provide space,
access to scientific equipment, connections to industry and
mentorship for IP management to startup companies. The
implementation of biotech parks and clusters, in particular, to
promote research and innovation, by establishing stronger
links between institutions active in life sciences & biotech and
pharma companies, innovative small and medium size en-
terprises, has over the past years proven extremely valuable to
attract companies, for example, in the area around Bangalore
with around 200 companies, or Genome Valley in the vicinity
of Hyderabad, with over 150 enterprises. Several more are in
the planning phase.

The Indian Government aims to stimulate the launch of
2000 startups in life sciences over the coming five years. It
is, however, uncertain how many of these will venture into
proprietary NCE projects, as so far drug discovery has been
considered the least attractive from an investment standpoint,
ranking last of 12 options, far behind diagnostics, medical devi-
escs, or discovery services. This low attractiveness is com-
pounded by structural weaknesses across the entire sector,
such as insufficient understanding of IP protection, regulatory
uncertainty regarding clinical trials, unethical practices, or pric-
ing uncertainties. All these contribute to raising barriers,
and therefore need to be fixed.

It remains to be seen if and how fast industry initiatives and
government efforts will be able to bring about the required
changes. In the meantime, the country has already scaled back
its highly ambitious, if not unrealistic, goal, which in 2010 had
been part of the government’s “Pharma Vision 2020”, to have
“one out of five to ten new drugs discovered in the world orig-
inating from India by 2020”, which would have represented
an average of at least three to six new medical entities (NMEs)
per year, to a more realistic, but still highly ambitious target of
“one NME per year and 10–12 incremental innovation launches
per year by 2030”.

The coming years will be critical. “Success will breed suc-
cess”, a statement made by one of the industry leaders at
a recent biotechnology convention in Hyderabad, might be
true, but it still requires success stories to initiate, then to fuel
the process.

Conflict of interest

The author declares no conflict of interest.

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