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# **Profiles of New Approaches to Improving the Efficiency and Performance of Pharmaceutical Drug Development**



**A Tufts Center for the Study of Drug Development White Paper**

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## Introduction

Biopharmaceutical drug development has been experiencing one of its most productive periods in recent history. During the past decade, the total number of new chemical and biologic entities in the R&D pipeline has been rising 6% each year and now exceeds 10,000 active drug candidates targeting unmet and under-served medical needs [1].

A variety of discovery technologies have helped drive growth in the drug development pipeline. To name a few: the speed of DNA sequencing has rapidly accelerated since the first genome was sequenced in the 1970s; high-throughput screening has resulted in a tenfold reduction in the cost of testing compound libraries; and combinatorial chemistry has increased 800-fold the number of new molecular entities to be potentially synthesized [1].

But throughout this productive period, the biopharmaceutical industry has had to manage a challenging operating environment characterized by increasing costs; inefficient and lengthy cycle times; and high levels of risk, uncertainty, and complexity. Total spending worldwide on biopharmaceutical R&D, for example, will reach a record \$140 billion (US\$) in 2014, representing a 4.9% compound annual growth rate during the past ten years [2].

Success rates in bringing a drug from discovery through to commercialization are low and getting worse. Recent Tufts Center for the Study of Drug Development (CSDD) research indicates that only 11.3% of drugs that enter clinical testing will be approved in the United States, down from a 16.4% success rate ten years ago. Since at least 10 years are required to bring a single molecular entity through R&D and approval, the total average capitalized cost to successfully introduce a marketed drug — including the shared cost of compounds that fail in development — now exceeds \$2.6 billion [3, 4].

Clinical testing phase durations have not improved since the early 1990s. The average clinical phase duration is 6.8 years and has increased 15% during the past decade. Longer clinical phase durations are in large part a function of the therapeutic classes that dominate research activity (e.g., oncology and CNS) as drugs targeting these diseases require more time to demonstrate safety and efficacy [3].

Tufts CSDD research has demonstrated that the rising cost and duration of drug development activity are a function of increasing protocol design complexity. The average number of procedures per protocol, average number of eligibility criteria, average number of investigative sites and countries where clinical trials are conducted simultaneously, have all increased dramatically during the past ten years creating more demanding protocols both scientifically and operationally [5].

Study volunteer recruitment and retention have also gotten far more difficult during the past decade. A Tufts CSDD study of several hundred global clinical trials found that biopharmaceutical companies must typically double the planned enrollment period to give their investigative sites enough time to recruit study volunteers and complete a given clinical trial. Even with extended

clinical trial durations, one out of every ten (11%) investigative sites, on average, in any multi-center global clinical trial will fail to enroll a single patient and one-out-of-four (39%) will under-enroll [6].

Biopharmaceutical companies have not idly accepted the growing challenges to the development of new drugs. Companies are using a wide variety of innovative approaches to adapt the R&D and manufacturing process to the changing scientific landscape. These innovative approaches to drug discovery, development, and manufacturing shed light on a resilient enterprise making progress in improving the quality, performance and efficiency of R&D and manufacturing. This paper examines some of these approaches and provides profiles of actual examples being implemented by biopharmaceutical companies in the U.S.

## Background

The initiatives profiled in this paper were developed by the research team at the Center for the Study of Drug Development at the Tufts University School of Medicine (Tufts CSDD). During 2014, the team conducted an extensive literature review following by nearly three-dozen in-depth interviews with recognized experts and company representatives. Tufts CSDD also convened a roundtable to stimulate discussion and gather insights into the results from the literature review and interviews.

Established in 1976, the Boston-based Tufts CSDD is an independent, academic, non-profit research group that assesses the nature and pace of pharmaceutical and biopharmaceutical innovation. Tufts CSDD's multidisciplinary research staff conducts grant-funded research that informs R&D strategy, practice and public policy affecting the development and regulation of new medicines. The results of Tufts CSDD research has informed Congress, the National Academies of Science, foundations, the National Institutes of Health, the pharmaceutical and medical device industries, capital market analysts and investors, the Food and Drug Administration and the Department of Health and Human Services, and regulatory agencies and policymakers around the world.

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## Approach One: TARGET VALIDATION

### Promise and Opportunity

- Greater accuracy in identifying and selecting the most promising drug candidates;
- Improvement in clinical-phase success rates;
- Reduction in the cost of animal models and in combining individual pre-clinical assessments.

The target validation process tests individual molecules and genes associated with normal physiology and disease to identify pathological structures for the experimental treatment to act upon. Target validation has historically been a very time intensive process involving extensive batteries of tests to assess the toxicology, pharmacokinetic/dynamics, bioavailability, and metabolism of drug candidates [7].

Information gathered during target validation has also not translated well to drug development decision-making. Even with promising pre-clinical results, most compounds — nine out of ten — will fail during clinical trials leading up to regulatory approval. At the present time, companies are typically often unable to accurately predict a compound's success or failure prior to conducting early testing in humans. As a result, research sponsors typically must make substantial investments to support fixed and variable non-clinical and clinical research costs.

Improving the target validation process earlier in the R&D process would inform critical decisions about which compounds to take into clinical research and those to be terminated. As a result, more effective target validation holds promise in improving later-stage R&D success rates and in conserving valuable R&D resources.

New advances in target validation — including platform technologies — are giving scientists better data quality, offering more accurate insight and predictive power and greater confidence in non-clinical findings, which in turn leads to more prudent R&D resource and investment allocations.

The human genome project was the catalyst behind the creation of several new scientific fields including genomics (i.e., studies of genomes) and proteomics (i.e., studies of proteins) that improved understanding of physiological systems, both natural and pathological, and potential targets for new drug therapies [8]. At the same time, the human genome project introduced many new complexities to drug discovery. Genomics and proteomics are resource intensive and require sophisticated analyses that can be applied to biomarker discovery in particular diseases [8]. The type of information generated from these analytical practices is critical to current and future R&D efforts. Scientific understanding of epigenetic mechanisms — biochemical processes to alter genetic activity without affecting genetic sequences — has also improved. This has resulted in the identification of new sources of potential drug discovery targets [9].



New approaches to target validation require advanced technology solutions as well as open collaborative models. Risk-sharing arrangements and pre-competitive collaborations are becoming more common as pharmaceutical companies recognize the rising cost of more sophisticated target validation and the opportunity to reduce redundancies and leverage talent and knowledge through partnership. More than 300 global consortia have formed between 2005 and 2014 to share data, expertise and resources to support more collaborative global drug development activity. The number of consortia formed is nine times that formed during the prior five year period. The Biomarkers Consortium, the Predictive Safety and Toxicology Consortium are but a few examples of open innovation collaborative models supporting target validation specifically. Companies can no longer successfully sustain every asset in their portfolio [9]. The new approaches to target validation necessitate collaboration and partnering and these offer promise for achieving greater progress in research efforts.

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## PROFILE: SANOFI

### *Pioneers in Organ-on-a-Chip Platform*

Sanofi is one of the first pharmaceutical companies to establish key partnerships and to invest resources in efforts to validate the microchip-mounted “Organ-on-a-chip” platform for pre-clinical research. Primarily based on microfluidic principles, “organs-on-a-chip” are miniaturized models of human organs and organ systems whose channels can be lined with various human-derived cells.

Sanofi’s Senior Director of Standards and Innovation within Pre-clinical Safety believes that this platform will enable all companies to make more informed and confident decisions sooner, to improve product attrition rates and to help companies use resources and investment capital more efficiently [10]. Sanofi has entered into a number of partnerships focused on validating the Organ on a Chip platform technology. Sanofi is assisting two companies — Zyoxel, a human tissue testing technology company, and Hurel, a bioanalytic tools company — in validating their microfluidic-based products. Sanofi has provided grant funding to the Massachusetts Institute of Technology to support microfluidics innovation. Sanofi recently established a partnership with the Wyss Institute of Biologically Inspired Engineering at Harvard University, an academic group with deep expertise and numerous patents in Organ-on-a-Chip platform technologies [10–12]. According to Sanofi’s Senior Director of Standards and Innovation, there has been more data on target validation available, especially for drug metabolism and PK (pharmacokinetics), and the ability to predict with certainty toxicology and metabolism. These play a critical role in establishing clinical outcomes [10].

The work Sanofi is conducting complements early work by the NIH, FDA, and DARPA [15,16]. The agencies have previously collaborated on an initiative for the development of tissue chip models to improve the process for predicting drug safety. These three regulatory bodies have pooled their resources to enable funding opportunities through the Microphysiological Systems program led by the National Center for Advancing Translational Sciences (NCATS), which is enabling additional academic groups across the country to further develop the “organ on-a-chip” technology [17].

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**PROFILE: TAKEDA*****Open-Access and Pre-competitive Consortia***

Takeda has been an active member and supporter of the Structural Genomics Consortium (SGC), an open-source pre-competitive consortia dedicated to improving basic scientific understanding of the biology of major diseases including cancer, HIV, Alzheimer's, autoimmune diseases (e.g., rheumatoid arthritis and lupus) and type 2 diabetes [7, 13].

With the support of Takeda and other members, SGC has characterized 15% of all human protein structures for use by the research community and the public. And SGC is generating characterizations of three novel molecules each quarter [14]. Takeda hopes that its support of SGC, and that of other organizations, will help accelerate the time to validate target molecules and will make data accessible in the public domain earlier in the process to engage other scientists, health professionals and patients in achieving progress needed to develop new therapies..

## Approach Two: ENHANCING IT INFRASTRUCTURE

### Promise and Opportunity

- Greater efficiency in translating drug discovery and pre-clinical data into clinical research activity;
- Greater efficiency in translating clinical research data into clinical practice;
- Lower cost and improved efficiency in prospectively identifying investigators, investigative sites and clinical trial participants;
- Improved effectiveness and speed in identifying new treatment pathways, new mechanisms of action and targeted patient subpopulations that may best respond to new treatments.

Patient reported outcomes data from clinical trials and from real world clinical settings can provide invaluable information on the benefits, risks and impact of new medical therapies. This data also informs many other functions including study design and market positioning.

Data sources are multiplying at a rapid rate both within and outside biopharmaceutical companies. New data collected during the R&D process is being combined with structured (e.g., clinical and health outcomes data) and unstructured (e.g., patient and caregiver reported outcomes data; payer and provider reported experiences) data. Real-time and predictive analytics built around these data have the potential to generate valuable insights and to facilitate higher quality and more efficient drug development.

Biopharmaceutical companies are increasingly using real world evidence with the objective of achieving greater understanding of patient populations to advance current and future treatment options for patients. Companies are utilizing novel approaches and technologies to integrate, store, interrogate and analyze large datasets from multiple sources. Real world data will ultimately be used to develop more targeted therapies and personalized medicines.

The use of both structured and unstructured data and data analytics are being used across all industries to generate value. Unstructured data is information that is not housed in a database and can potentially be of great clinical benefit when converted to an electronic system. There is a vast amount of unstructured healthcare data that is currently being mined by biopharmaceutical companies. Strategies have included developing platforms for warehousing and analyzing everything from pre-clinical and translational data to electronic health records (EHRs) and claims data. Currently, these data warehouses exist largely independently. The goal for the near future is to link all of these disparate sources of data within and across organizations. The knowledge gained from data collected during discovery through clinical testing, combined with data from patient registries, EHRs, and health insurance claims, is expected to accelerate and optimize the R&D process.

McKinsey Global Institute estimates the US healthcare system could generate \$100 billion in value in a given year by integrating data sources [14].

Patient registries contain data from individuals with similar disease states and can vary in the type of data that is collected. EHRs, or electronic health records, contain patient medical data while insurance data is information on claims that are paid. These sources of data are typically referred to as real world evidence resulting from commercial medical therapies and they are accessed by biopharmaceutical companies through collaborations with academic medical centers, health systems and payers.

Protecting patient privacy and confidentiality, breaking down siloes and navigating control and ownership of data are some of the central challenges that companies face when working with external partners to gather real world data. Integrating data from electronic health records is not easy as many of the fields are incomplete and billing, pathology, and lab data may not be integrated with the rest of the medical record. In addition, for these data sources to be applied to drug development, qualified researchers from the private sector, including biopharmaceutical scientists, will need to have access to the data for research purposes. Some of the challenges to data integration are gradually being overcome as biopharmaceutical companies work together with government agencies, academic, and IT sectors [10].

To mitigate the challenges the research ecosystem must evolve from the current state into a learning healthcare system as has been suggested by the Institutes of Medicine [10]. This is a system characterized by “continuous learning and a much more dynamic approach to evidence-based development and application” [10]. Creating a new clinical research paradigm would include universal electronic health records and tools for database linking, mining, and use [10]. This new paradigm comprises a continuous and timely source of information that can impact all stakeholders across the healthcare continuum.

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## PROFILE: LUNDBECK

### *Integrated Data Management System*

All biopharmaceutical companies have a corporate database for their pre-clinical data. These corporate data warehouses contain data from chemistry, biology, pharmacology and other drug discovery disciplines but do not traditionally perform any data transactions between these areas [11]. Since the 1980s, Lundbeck has combined compound and assay results, and data from analytical procedures for screening compounds critical for drug discovery. The company has gradually developed a new data management system. The database has been expanded by the in-house research informatics team of seven dedicated programmers to provide data storage and retrieval, and also incorporates decision and workflow support.

This unique enterprise research data management system is called Life Science Project (LSP) at Lundbeck. It is one coherent system built on top of one database that includes everything from data on genes,

animals, and compounds to late-stage exploratory toxicology studies [11]. Having an integrated data management system is critical to improving knowledge at the pre-clinical stage and can potentially speed up the process of drug development. In addition, this system promotes cross-collaboration and facilitates cross study analysis which can ultimately lead to improved clinical outcomes.

All logistics are handled in the system such as registering reagents, plants and animals, and re-ordering. Lab equipment is connected to the database such that controlled file transfers to the equipment can be managed, progress can be monitored remotely and output data can be captured directly. The same system can be used by external chemistry partners such as chemists at CROs to register new compounds into the database. Discovery project managers can engage in data mining and order new tests when they have decided which compounds to move forward [11]. Such a system can potentially improve efficiencies within discovery and speed up the process of moving a compound forward in development.

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## **PROFILE: JANSSEN (JOHNSON & JOHNSON)**

### ***Collaborative Translational Research Platform (tranSMART)***

In 2008, the Immunology, Oncology, and Biotechnology R&D sections of Janssen began a data collaboration that broke internal silos across therapeutic areas, as well as brought together knowledge from drug discovery and development processes [52]. In June 2009, the R&D Informatics group at Janssen launched a translational data warehouse and analytics platform called tranSMART that contained curated information from genomic and proteomic experiments as well as clinical trials. The human genome project was the catalyst behind the creation of several new fields that have provided more sophisticated means of understanding physiological systems, both natural and pathological, in reference to potential targets [4]. The data warehouse and related querying and visualization tools allow scientists to quickly re-validate hypotheses and generate new ones. Data can be queried by compound, disease, gene, gene list, pathway, and gene signature. By typing in a gene, a researcher can see every related clinical trial, gene expression datasets where expression of that gene was significantly altered, literature results, pathway analysis, etc. [4]. The data warehouse has immense value as it allows scientists and clinicians who design clinical trials to have information that can potentially speed up the drug development process.

Janssen then made a strategic decision to develop the software in an open-source, cloud-hosted environment to stimulate and support collaborations with external partners. Early on they partnered with the Cancer Institute of New Jersey for their informatics and medical expertise. Gradually, the collaborations grew to such an extent that in 2013, the tranSMART foundation was established for coordinating the development of the next generation of tranSMART organizations. These organizations include 20 global life science organizations such as biopharmaceutical companies, universities and academic medical centers, disease and patient advocacy groups as well as government entities [52].

Each partner contributes new perspectives and data and increases the likelihood of translating scientific discoveries into medical breakthroughs that address unmet patient needs [52].

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## PROFILE: ASTRAZENECA

### *Real World Evidence Health Collaborative*

In 2011, AstraZeneca partnered with HealthCore, the health outcomes research subsidiary of WellPoint, Inc. Through this partnership, patient administrative claims data can be linked with lab results data and electronic medical record data to develop a longitudinal patient record. These data provide important insight to population health, unmet medical needs, the burden and cost of illness, treatment pathways, and the safety and value of specific therapeutic options [21].

The Collaborative conducts prospective and retrospective studies using comparative effectiveness research and observational data as well as patient and provider surveys. AstraZeneca has utilized the database to build endpoints or targeted outcomes into their clinical study protocols so those endpoints that are important to payers can be included in the clinical trials from the beginning. Existing products are being studied to help payers determine safety and value of drugs by combining real-world evidence and comparative effectiveness research [21].

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## PROFILE: PFIZER

### *Real World Data Initiative*

At Pfizer, real world evidence is being used to answer three key questions:

- What are the right targets for drugs based on our biologic understanding?
- What are the right attributes needed for new treatments?
- Can we identify the right subgroups of patients who will benefit the most from new therapies? [22]

With these questions in mind, Pfizer has entered into partnerships with three different collaborators in recent years including Medco, a pharmacy benefits management company that is now part of Express Scripts. The goal of these partnerships is to effectively match patients with those treatments offering the most benefit. Data on specific patient populations and how they respond to treatments will help advance biologic and clinical understanding of drug targets.

Pfizer has also entered a partnership with the health insurance company Humana to improve measures of adherence, adverse side effects, and disease prevalence in key populations. In one collaborative study, data from chronic pain patients led to a predictive model of the type of patients at risk for opioid abuse. With this model, Humana can identify those patients and intervene early to protect patient safety and lower the cost of future treatments. Pfizer gains the benefit of fewer adverse reactions and better marketability of its drugs [36]. In addition, gaining knowledge of disease prevalence in specific populations can be invaluable for the advancement of new treatments.

A third partnership is with Humedica, a clinical intelligence company. The goal of this partnership is to harness de-identified healthcare data from disparate IT systems. The data gathered from electronic health records (EHR), practice management and claims data links information about patients from varied settings. The data can bring greater insight into patient needs and treatment effectiveness that can potentially lead to improving patient outcomes.

In February 2014, Pfizer joined the Optum Labs collaboration between Mayo Clinic and Optum (the research arm of UnitedHealth Group), with the goal of gaining insights into personalized medicine and testing new methodologies for analyzing real-world data [23]. Other members of this collaboration include the American Medical Group Association, Boston University School of Public Health, Lehigh Valley Health Network, Rensselaer Polytechnic Institute, Tufts Medical Center and the University Of Minnesota School Of Nursing.

Another innovative step that Pfizer has taken is the creation of a Data Mart that allows all appropriate groups across the Pfizer enterprise to access real world data sets [24]. There are three therapeutic areas: oncology, autoimmune disease, and pain where the use of real world data can lead to a potential increase in new patient therapies and improved patient outcomes. Sharing data cross-functionally and across these therapeutic areas allows for unprecedented collaboration and learning across the organization, that can potentially lead to the development of more effective treatments.

## Approach Three: ADAPTIVE TRIAL DESIGNS

### Promise and Opportunity

- Improvement in late stage success rates through more accurate dose response assessment;
- More effective identification and targeting of patient subpopulations;
- Greater efficiency in adapting and amending study designs;
- Reduction in direct operating costs as a result of early terminations due to safety and efficacy futility.

Adaptive trial designs have the great potential of improving success rates and optimizing clinical trial performance and data quality. Adaptive trial designs enable drug developers to conduct simulations and more upfront planning and review activity prior to beginning actual testing with study volunteers [25]. Protocols are modified, while the clinical trial is underway, through interim data review. As a result, adaptive trial designs enhance R&D efficiency because the need to repeat trials that closely miss their clinical end-point or fail to identify the correct dose is eliminated. Early clinical trial terminations due to safety or efficacy futility allow companies to re-allocate resources to more promising drug candidates [26].

R&D quality is enhanced under adaptive clinical trials, where dose assessments can assist research sponsors in more accurately identifying the right dose for the right population. This is particularly valuable when companies conduct adaptive dose response assessments in early stage clinical trials prior to entering larger, later stage clinical trials. Adaptive clinical trials also help to get the right drug at the right dose to each patient more quickly. [27].

Despite the potential benefits, additional work is needed to identify the most effective uses and approaches to adaptive trials design. The challenges include concerns about how to monitor data without introducing bias; data management, delays and disruptions in execution, patient participation and the distribution of clinical supplies. However, these challenges are being mitigated as internal teams and external contract research organizations gain more experience in supporting adaptive trial designs and as infrastructure and technologies advance.

Some simple adaptive trial designs, such as early study terminations due to futility, are increasingly being adopted and are currently found in approximately 20% of Phase III clinical trials. Sample size re-estimation, or re-calculating the sample size of patients needed for a clinical trial based on interim trial data is also a relatively simple adaptive design [26]. Although the use of adaptive approaches in early clinical stages would have the greatest impact, sophisticated adaptive designs such as dose-finding studies and randomization ratios are currently implemented in less than 10% of clinical trials [26].



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**PROFILE: ELI LILLY*****Advanced Analytics Hub***

Eli Lilly has been implementing simple adaptive trial designs since the 1990s, but has recently made in-roads with more advanced designs supported by computer simulations and modeling [27]. Given their venture into this area, they expect to gain substantial benefits from this innovative approach. In 2010, the strategic decision was made to form a group within the Global Statistical Sciences function called the “Advanced Analytics Hub.” The Hub consists of a team of statisticians dedicated full-time to advancing each of the following five key areas: Clinical Trial Optimization, Tailoring Analytics, Bayesian Methods, Data Mining, and Modeling and Simulation. [28].

The Clinical Trial Optimization group has focused on planning and implementing adaptive trial designs and the team that supports this area includes individuals from data sciences, information technology, clinical supplies and regulatory science. Before implementing a given trial design, virtual clinical trials are run on sophisticated simulation engines which take into account statistical design, analysis and trial execution options, such as enrollment rate and drop-out rate, in order to determine which trial design is most advantageous [29]. The metrics used to determine this are called “information value” and take into account decreased uncertainty of outcome per unit of time and cost expended. Recently, Lilly has increased its emphasis on multi-dimensional optimization, where adaptations focus not only on the primary efficacy measure but on every important measure within the trial.

With support from the Hub, the use of Bayesian methods as a statistical approach, in which the research design of a trial can be altered has also increased. The impact of Bayesian methods in adaptive designs is measurable and Lilly estimates that with the implementation of sophisticated adaptive designs such as a seamless Phase I/II trial, they can expect a cycle time reduction in the range of 9 months to 2 years [26].

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**PROFILE: BIOGEN*****Adaptive Dose Finding Studies***

At Biogen, developing adaptive trial designs is a key focus of the company's biostatistics department [25]. The first adaptive trial was planned in 2012 and the estimated final data collection date for the primary outcome measure was third quarter of 2014 [25]. The current adaptive design allows Biogen to evaluate the efficacy of an experimental drug at five different doses, whereas the original plan was to only explore three doses with a traditional design. An assessment of each dose was performed to see which doses exhibited the highest utility which therefore allowed for termination of other less effective doses earlier in the trial. One potential advantage of using the adaptive design is the increased likelihood of taking the right dose to Phase III, if efficacy is established. By improving Phase III dose selection, adaptive designs can ultimately provide efficacy assessment earlier and improve upon late stage success rates.

Following the implementation of this first study, there has been increased response from other research teams within the company hoping to add adaptive elements to their trials and several other adaptive trials currently being discussed [30]. Biogen is now in the process of expanding their computing capabilities, statistical personnel, and other internal resources in order to provide its adaptive trial design management capabilities more broadly.

## Approach Four: GREEN MANUFACTURING PRACTICES

### Promise and Opportunity

- Reduced carbon footprint and environmental impact;
- Lower manufacturing and operating costs;
- Increased manufacturing efficiency and safety.

Green manufacturing is an operating strategy focusing on streamlining processes and reducing the use of resources, including energy and water, to lower operating costs and improve efficiency. Green manufacturing also benefits the environment through advanced waste management and reduced carbon footprint. It has touched all economic sectors and is already having an impact among pharmaceutical companies around the world [31].

Green manufacturing targets a number of critical areas including chemical synthesis, drug production and packaging, waste management and resource utility. Biopharmaceutical companies have long been committed to supporting environmentally responsible operating practices. Many companies have stepped up their efforts to implement more advanced and integrated enterprise wide approaches. As part of these efforts, companies have developed new corporate policies and responsibilities that reflect their commitment to green practices and they are gathering new metrics to determine the impact on the environment.

Johnson & Johnson and GlaxoSmithKline were early proponents and adopters of green manufacturing [32, 33]. At this time, nearly all mid-sized and major biopharmaceutical companies are investing in sustainable green manufacturing practices. And a majority of companies now produce corporate responsibility reports that include information on environmental impact and what steps are being taken to achieve new goals above past baseline manufacturing performance and cost measures. The variability between current and past manufacturing metrics guides management decisions about where to focus future investments in manufacturing process enhancements. Examples of incremental manufacturing improvements include:

- Retrofitting or building new facilities that set higher standards for energy, water, and waste management [32].
- Implementing green chemical pathways that are more energy-efficient and better at recycling original solvents and reagents and reducing the likelihood of work-related toxicities.
- Incorporating continuous processing, single-use bioprocessing equipment, co-generators, leading to increased sustainability [34-36].
- Improving bioprocessing approaches to accommodate more streamlined, on-demand manufacturing.

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## PROFILE: GLAXOSMITHKLINE

### *Pioneering Efforts in Sustainability*

GlaxoSmithKline was among the earliest green manufacturing pioneers to address sustainability and optimized practices. Early on, the company applied new manufacturing metrics to achieve greener practices and examine the use of materials including solvents – the chemical processes used in drug manufacturing. Later, GlaxoSmithKline implemented the Life Cycle Assessment (LCA) green engineering approach to introduce and integrate more efficient practices across the continuum of manufacturing supporting R&D through commercialization [33, 37].

GlaxoSmithKline created and shared the first green solvent selection guide to assist industry-wide decision-making. A 2009 LCA attributed approximately 75% of overall energy needed to produce an active pharmaceutical ingredient (API) to the solvents used [33, 38]. By focusing on solvent selection and manufacturing catalysts (which can carry out a single reaction many times), GlaxoSmithKline maximized resource efficiency, reduced environmental impact and lowered manufacturing costs. The company explored bio-catalysis manufacturing and successfully developed a more efficient synthesis route for one of its drugs. GlaxoSmithKline also explored continuous processing technology in a pilot program as an alternative to batch processing [39]. It is a system of continuous manufacturing of chemicals to consume less resources. In this pilot program, technology solutions are used to conserve water and solvent use. The company has stated publicly that this pilot program has reduced water use by 83% and solvent use by 42% leading to a 52% overall reduction in conversion carbon footprint [39]. The success of this pilot program led to a recently announced decision to construct a new manufacturing site utilizing continuous processing technology [24].

GlaxoSmithKline has achieved its initial goals and continues to make progress in green engineering and manufacturing. Compared to baselines established in 2010, the company has set in motion plans to reduce its carbon footprint by 25%, water impact across the value chain by 20%, and operational waste by 50% all by 2020 [41]. Water consumption and wastewater production have already fallen by 2.5 million cubic meters and 1.4 million cubic meters, respectively.

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**PROFILE: CELGENE*****Improving Facility Environmental Sustainability***

Since 2008, Celgene has been working to identify the key contributors of its direct (on-site) and indirect (produced externally) green-house gas emissions. Celgene has established key milestones it hopes to achieve every 5 years through 2025, beginning with problem identification followed by the development of new methods – including energy usage, waste management, transport emissions and logistics, and water consumption — to reduce the emission of green-house gases [42].

Celgene has already begun implementing changes that will increase facility efficiency, and reduce their carbon footprint while lowering manufacturing costs. Celgene has retrofitted two facilities and constructed another from the bottom up to support sustainability [42]. The new facility in San Diego, CA has been designed and constructed with the goal of achieving Leadership in Energy and Environmental Design (LEED) accreditation, a green building certification which they obtained in April 2013 [42]. Eco-friendly facilities like this one in San Diego promote energy efficiency, reduce waste, and strive to minimize environmental impact through conserving natural resources and minimizing pollutants.

Designing and modifying manufacturing facilities to support green practices are an expensive undertaking that requires companies to continually quantify the many benefits that come from reducing waste production, improving resource and waste management, providing safer working environments for employees, and lowering operating costs. In a recent Carbon Disclosure Project report, Celgene indicated that it expects a return on green manufacturing investments to range from less than one year to ten years [43].

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**PROFILE: ABBVIE*****Reducing Potential Waste in Manufacturing Practices***

AbbVie has undertaken a range of facility-specific and company-wide initiatives to optimize its manufacturing operations. AbbVie's Vice President of Environmental Health and Safety (EHS) explained that its manufacturing operations are a critical means by which the company hopes to improve its carbon footprint [36, 44]. AbbVie expects to realize manufacturing cost savings and achieve higher levels of efficiency while simultaneously optimizing its manufacturing practices.

AbbVie has set company-wide goals to reduce waste production by 20% by the year 2020 [29]. The company has already executed a number of programs and enhancements to reduce waste production and to leverage renewable energy (e.g., solar panel and co-generation systems) [20]. Even with growing production levels to meet global demand, since 2010 Abbvie has reduced waste associated with manufacturing by 6%.

## Concluding Remarks

One of the largest causes of delays in drug development is due to challenges related to patient recruitment and retention. To address this challenge, pharmaceutical and biotechnology companies are exploring new channels to reach, educate and engage patients. The widespread use of social media among the general population has encouraged companies to use this channel to more accurately reach and partner with patient communities.

At this time nearly all major and mid-sized pharmaceutical and biotechnology companies have developed corporate guidelines to address employee use of social and digital media. With regards to use of these platforms to support outbound communication, sponsor companies are primarily distributing information for commercial purposes (e.g., about drugs, diseases, and the company) and to learn from patient and professional conversations about marketed products [46].

## Emerging Trends

In R&D, use of social and digital media communication channels is far more limited. A majority of research sponsors report posting patient recruitment ads on social media websites [46]. Less than 20% of companies—including Pfizer, Roche and Lilly—have used social media to ‘interactively’ engage with patients, and they have done so largely on a pilot basis [47-49]. There are company concerns about needing to comply with FDA guidelines regarding communications with health professionals and that potentially discourages the willingness and use of social media more broadly by companies. Pharmacists and other trusted health educators are increasingly being used as another communication channel, though this too has been on a pilot basis [50]. This channel is one of the most accessible to patients, particularly those in more remote communities. Americans visit pharmacies at more than five times the annual rate at which they visit their primary and specialty care physicians combined. Pharmacist-patient interactions are likely to increase as pharmacists become more involved in patient care, including their expanded roles in managing medication therapies and chronic diseases [51].

Pharmaceutical and biotechnology organizations have been reluctant to widely adopt these approaches due to concerns about protecting patient privacy and confidentiality and about adversely impacting research integrity and data quality. As companies gain experience and as they develop policies and guidelines, the use of these channels is expected to increase significantly. And in the process, these channels will become valuable new ways to amplify the voice of the patient and provide greater access to information that will help a larger number of patients find new treatments.

The approaches profiled in this paper represent exciting and innovative solutions being implemented across the biopharmaceutical industry to improve R&D and manufacturing quality, efficiency, and performance. The approaches increasingly draw their inspiration from the broader health care environment and from other industry sectors. They are all framed by the strong desire to better serve

the public and patient communities. And they are highly collaborative, relying on the sharing of pre-competitive information among public-private consortia and the community of biopharmaceutical companies.

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