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Case study: impact of technology investment on lead discovery at Bristol–Myers Squibb, 1998–2006

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We review strategic approaches taken over an eight-year period at BMS to implement new high-throughput approaches to lead discovery. Investments in compound management infrastructure and chemistry library production capability allowed significant growth in the size, diversity and quality of the BMS compound collection. Screening platforms were upgraded with robust automated technology to support miniaturized assay formats, while workflows and information handling technologies were streamlined for improved performance. These technology changes drove the need for a supporting organization in which critical engineering, informatics and scientific skills were more strongly represented. Taken together, these investments led to significant improvements in speed and productivity as well a greater impact of screening campaigns on the initiation of new drug discovery programs.

Introduction

Identifying compounds that bind to and modulate biological targets implicated in disease pathways is a fundamental step in the drug discovery process. The ability to screen tens of thousands if not millions of compounds in high-throughput bioassay formats has been a central focus for technology improvement in drug discovery over the past decade [1–3]. During this period a wide range of technological innovations were developed, including the assembly of large collections of compounds [4], fully automated compound storage and retrieval systems [5,6], novel assay design approaches [7,8], automated screening systems [9,10] and informatics systems that enabled facile data retrieval, analysis and integration [11]. The identification of screening leads took its place alongside other innovations such as functional genomics [12] and *in vivo* knockout technology [13] as an essential tool in the discovery [14] and validation [15] of new biological targets. The main aim of all these technology investments was to increase productivity, efficiency and eventually overall success rates in Discovery research. This review will describe a series of technology investments from 1998 to 2006 at Bristol–Myers Squibb and attempt to assess their impact on the drug discovery process.

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Analysis and strategy

The goals set by Bristol–Myers Squibb Drug Discovery in the late 1990s included an overall desire to increase capacity, improve timelines and ensure better success rates [16]. An internal review in 1998/1999 revealed variable turnaround times from assay design to completion of an HTS campaign (on average 28 weeks but many examples of greater than 40 weeks), low screening reproducibility rates and screening and data processing capability that was unable to support the full scope of therapeutic area research. Most significantly, screening campaigns had little impact on discovery programs, providing few new structures as starting points or insights into emerging structure–activity relationships (SARs). Analysis at that time indicated only 20% of programs were positively impacted by leads from screening. The compound management system was heavily biased towards manual processes and the screening deck was judged to be limited in size and diversity (the 1998 screening deck consisted of approximately 50,000 compounds). The utility of the deck was further diminished by a lack of process and organizational integration between compound management and the various HTS groups. These findings led to the introduction of a new strategy aimed at significantly improving productivity and efficiency in Lead Discovery

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through technological innovation. The main pillars of the technology strategy were as follows:

(1) Develop an integrated compound management platform for storing and distributing compounds.
(2) Build a large, diverse and high-quality compound collection.
(3) Construct a fully integrated screening capability supported by an optimally staffed organization
(4) Streamline and integrate discovery workflows with an overarching informatics infrastructure.

The strategy involved building a robust, centralized infrastructure of stable technologies with a high probability of working reproducibly over many years. During this time, several speculative, 'bleeding edge' technologies, despite their apparent high potential, were evaluated and set aside.

Compound management

Newly synthesized compounds had traditionally been handled by *ad hoc*, manually intensive processes that included local storage and distribution of compounds among program scientists. The perceived advantages of rapid compound delivery were offset significantly by restricting access to compounds for use in screening or by the wider discovery community. The central compound distribution organization used minimal automation and was thus dependent upon substantial numbers of staff to carry out its role. The compound collection available for screening at any one time was not more than 50,000 compounds of unknown purity and stability. Building a new compound management system required a radical overhaul of skill sets, organizational structure, compound flow processes and technology [17].

Compound storage and distribution

The centerpiece of the new compound distribution system was Haystack, a custom-built, fully automated compound management and retrieval system, installed during 1999. The new system had the capacity to store 750,000 dry compound vials and 5 million individual tubes at 4 °C in two independent storage wings. Once the existing compound collection had been transferred and the Haystack was fully operational, a new paradigm for storing and distributing compounds was implemented which continues to this day. Chemists are now able to weigh newly synthesized compounds into tared vials at the same time as their structures and identifying information are entered into the chemical registration system. At the compound dispensary, an aliquot is removed for solubilization and the remainder moved into the dry compound store. The tubes containing the solubilized sample are then moved into the tube store. The compound inventory system is instantly updated, and program scientists can immediately request sets of compounds in a variety of configurations, formats and concentrations for screening. All submitted compounds are incorporated into the high-throughput screening deck. Compound requests trigger a set of responses that result in compounds being dispensed, scheduled for assays, tested, results analyzed and data uploaded without further need for intervention from the project scientist. Uniform compound management policies are maintained at all geographically distinct BMS research sites.

Since the initial installation, the system has been augmented and upgraded by continuous investment in automation and state-of-the art software to meet the ever-changing Discovery environment. The store was retro-fitted with a series of automated platforms that supported the peripheral activities required for an integrated compound management workflow. These new capabilities required the development of an informatics infrastructure that allowed integration of additional automated platforms on the periphery of the central compound store, including automated weighing of compounds and vials, dissolution of compounds into solvents, capping and de-capping of tubes containing solubilized compounds and the preparation of serially diluted assay-ready plates.

Screening the compound collection

The approach employed to build the screening deck included compound recovery from BMS medicinal chemistry laboratories, targeted compound purchases from external vendors and construction of specific combinatorial libraries. The latter two tactics were guided by extensive computational modeling of critical biological target classes, such as G-protein-coupled receptors, ion channels, kinases and proteases to identify gaps in the compound collection. Existing and proposed compounds were evaluated for a range of drug-like properties and filtered to remove undesirable compounds [18], including false positives from ongoing screens that failed structural integrity evaluation. Acquisitions were subjected to rigorous LC/MS quality control for purity and integrity. The deck was arrayed in chronological order, which allows facile re-screening of targets when sufficient new diversity has been added to the compound collection. More recently, the main HTS screening deck has also been divided into a series of focused subsets of 30–60,000 compounds each designed around a target class such as GPCRs or kinases. These subsets can be created at minimum cost through careful planning of the screening deck replication process and are periodically upgraded with information from target class knowledge bases. This added flexibility enabled many exploratory targets to be screened in parallel and tool molecules to be identified. An important factor in maximizing the success of these smaller subsets was the application of computer modeling (3D pharmacophore and Bayesian) to select even smaller secondary subsets of compounds from the screening collection which had a calculated chance of being active against the target being screened [19,20]. Exploratory programs use these sets to find lead molecules or 'tools' to assist with target validation before full HTS campaigns are run.

High-throughput screening

Screening at BMS in the late 1990s suffered from a lack of robust screening technology, poor process integration, low capacity, high turnaround times and poor reproducibility of data. Many screens employed low- or medium-throughput assay technologies such as TCA precipitation, ligand-binding harvesting assays, multi-step ELISA, and other non-homogeneous approaches. All screens used 96-well plates as the test plate of choice and the automated systems that were running them were unreliable and prone to failing.

An overhaul of the entire system was undertaken, with planned investment in bio-assay technology, automation platforms and data analysis and visualization tools, accompanied by hiring and re-training staff with the appropriate multidisciplinary skills.

Screening automation

Our goal was to build system that would allow for continued expansion, growth and development of our screening capability for a decade or more, enabling fully automated, miniaturized screening in an informatics environment that would support data capture, analysis and reporting for even the most complex of assays. To achieve the required degree of flexibility for continuous, evolutionary growth, we decided to build the necessary informatics and hardware infrastructure with our own staff of mechanical, electrical and software engineers taking 'best in breed' technologies from the vendor community and assembling them into an integrated environment. In-house custom-developed solutions were then required to fill the gaps where no vendor solution was available. This activity was also supplemented by a joint project with Accenture called 'Enterprise' which helped elucidate our compound handling and screening processes as well as identifying our key informatics gaps. To the greatest extent, the new platforms would employ commercially available individual components, such as robotic scheduling software, robot arms, liquid handlers and micro-plate readers.

In the first phase of development (1998–2002), five fully automated systems were constructed that focused primarily on the integration of more modern instrumentation such as dispensers for addition of bulk reagents in the >10 μl range, imaging platforms for reading plates and plate transfer stations for 384-well compound transfer. These systems facilitated a seamless transition from assay design to production screening. By the end of this phase, all assays were run in 384-well plates and 50% were fully automated (the remainder being partially automated). It became apparent that informatics infrastructure would be the main factor limiting performance because of the rapid advances in screening deck size that were occurring simultaneously. HTS *Toolset*, a suite of custom-developed data analysis and visualization packages, was introduced in 2001. Using this system, data from an automated plate reader could be visualized via the informatics network within 10 min of the plate being read, eliminating error-prone manual data transfer and enabling real-time quality control and operator intervention in case of problems. Continuing enhancements to HTS *Toolset* functionality have steadily improved the productivity, reliability and quality of screening output.

The second phase of capability development (2002–2006), brought a focus on minimizing the costs associated with large-scale screening campaigns by means of further miniaturization of screening formats from 384 to small volume 384- and 1536-well plates. Several full-deck 1536-well HTS campaigns that were run in 2002 in workstation mode revealed numerous deficiencies in the infrastructure needed for low volume (2–5 μl) assays. The standard methods for delivering compounds in DMSO stock solution led to unacceptable DMSO final concentrations (above 1%, v/v). The only commercial technology for dispensing the required volumes (20–50 nl) at the time was pin-tools, which rely on surface tension to transfer tiny droplets but have inherently high levels of variability and require extensive washing between steps. Beginning in 2000, we collaborated with an instrument vendor to develop acoustic compound dispense technology [21], which uses ultrasound to dispense 2.5 nl droplets with high precision and accuracy in a non-contact manner. After a carefully controlled and risk-managed evaluation process, we adopted the technique as the standard for low-volume dispensing in all applications. Further innovations, including assay reagent addition down to 200 nl with a variety of liquid handlers and imaging technology that enables the simultaneous measurement of 1536 wells within a few seconds have led to ~80% of all assays being run in a miniaturized format (low volume 384 or 1536 plates) and 95% of assays under full automation.

Assay methods

Investment in new bioassay technologies [22], especially homogeneous assay methods, has been essential to realizing the full potential of the infrastructure improvements described above. We initially focused on full optimization of several standard formats including scintillation proximity assays (SPAs), time resolved fluorescence (HTRF) [23], FRET and absorbance formats. SPA assays [24], which were used for about 50% of our screening targets, are fully homogeneous and require only radiochemical labeling (^{3}H, ^{125}I, ^{33}P) of ligands or substrates, rather than attachment of the large fluorescent tags required by other formats. However, traditional serial PMT-based scintillation counters required read times of over 40 min per 384-well plate. This limitation was overcome by using beads compatible with plate imaging readers, which reduced read times to less than 5 min per plate. Despite the disadvantages associated with handling radiochemicals, the new SPA approach allowed faster reagent construction times, more efficient assay design and the avoidance of interference with fluorescent molecules in the screening deck. Till date, these assays still constitute 20–25% of the HTS campaigns run each year at BMS.

Other homogeneous assay formats employing luminescent, fluorescent or absorbance readouts pose two significant challenges. First, many compounds in the screening deck absorb or fluoresce in the same wavelengths as the assay signal is being measured. This leads to difficulty deciphering the results and can give misleading data resulting in hits being missed or falsely detected. Second, the need to generate sufficient signal for good precision using these formats can lead to enzyme assays being run to inappropriate levels of product formation that may obscure results for weak inhibitors. Both of these challenges can be addressed by using kinetic-read assays that take multiple measurements from the same well over a short period of time (5 min) in order to calculate true initial reaction velocities. This method requires very little signal, and compound interference is significantly reduced because interfering compounds have a net effect on signal which does not change over time.

Finally, miniaturization of calcium flux assays was enabled by the development of luminescence imaging-based Aequorin technology [25], which has overcome the limitations of older instrumentation that dispensed ligand to cells and measured the response via laser excitation of a fluorescent dye. The combination of Aequorin technology with acoustic compound dispense systems has enabled us to routinely run 1536-well cell-based assays in a 2 μl assay volume.

Staff skills and organization

An overall change in the manpower composition of the screening organization proved to be essential in realizing maximum value from our technology investments. Fewer technical staff were needed to carry out manual operations, allowing their replacement by

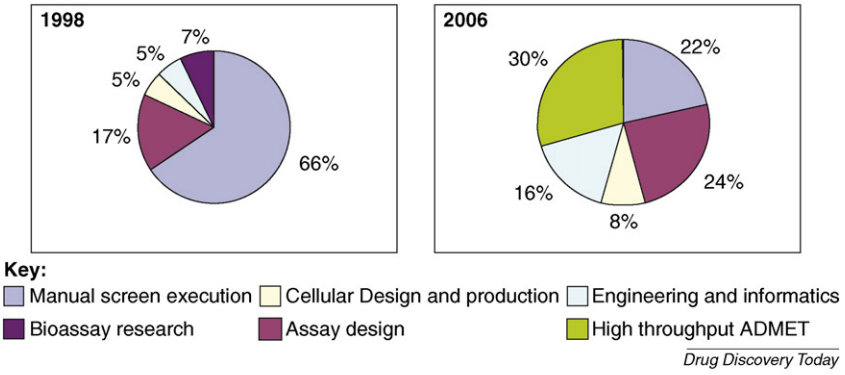

FIGURE 1

Manpower functions within lead discovery at BMS.

biochemists, enzymologists, receptor pharmacologists and cell biologists, all with expertise in high-throughput screening and drug discovery. In parallel, we built a team of software, electrical and mechanical engineers to construct enhance and maintain the lead discovery infrastructure. The change in skill sets in the Lead Discovery organization at BMS over an eight-year period is shown in Fig. 1. The significant gains in efficiency because of transfer of assay plate replication to the highly automated compound management function and increased automation of screen execution allowed a 50% reduction in the overall number of staff needed to run the screening operations. A significant proportion of the reallocated staff was then used to build a high-throughput ADMET group to support structure liability analysis for drug discovery programs.

Assessment of impact

Recently, there has been a widespread perception that overall productivity as measured by the rate of introduction of new medicines has declined [26,27]. Several commentators have used the productivity decline as a rationale for debating the wisdom of technology investments such as those described here [28,29]. Although this view fails to fully recognize the extremely long development cycle for new drugs, we believe that there is a need for some assessment of the impact of advances in lead discovery technology on drug discovery. We offer the following examples to show that increases in operational efficiency at BMS over the past eight years have led to significant improvements in the ability of HTS to influence the direction of new discovery programs.

The current BMS compound archive now consists of over 1.2 million proprietary and non-proprietary compounds – a 24-fold increase since 1998 (Fig. 2A). The number of total samples distributed to the Discovery organization increased 30-fold while manpower utilization has become increasingly efficient (Fig. 2B, data only available from 2000). Migration of routine compound handling from both screening and therapeutic area functions to the centralized compound management system has greatly improved efficiencies in the discovery process, reduced the time for access to compounds and increased the overall quality of samples and data that are driving lead identification throughout drug discovery.

Figure 2C demonstrates that the number of wells run for each target has increased almost 30-fold since 1998. Time for screen completion has significantly improved despite this increase. In addition, the criteria for screen completion now include comprehensive characterization of screening hits including concentration response curves, selectivity profiles and physicochemical data. From 2005 onwards, screening campaigns were increasingly likely to utilize target-class focused subdecks rather than the entire collection, leading to an overall decrease in the average numbers of wells screened between 2005 and 2006. However, significantly more concentration response curves are now run per screen (from less than 100 in 1998 to approximately 5000 in 2006), and later campaigns have often included simultaneous counter screening for selectivity. Despite these significant increases in both the quantity and quality of data output, the number of FTEs needed to carry out HTS operations (as measured by the FTEs per 100,000 compounds screened) has steadily diminished (Fig. 3). At the same time, the trend toward greater miniaturization was able to mitigate the growth in consumable and reagent costs resulting from the larger number of wells screened.

The most significant and yet difficult metric to measure is overall impact of screening on programs. This trend is illustrated in Fig. 4, which shows the percentage of screens completed each year by category of impact. The most stringent criterion for favorable impact – 'enabling contribution' – is applied only to screens that supplied the structural starting point for programs that received a significant manpower commitment for lead optimization as a result of formal management review. A 'significant contribution' indicates that screening hits informed the development of structure–activity relationships during lead optimization. All other outcomes are grouped as 'data provided'. No allowance has been made in this analysis to reflect the perceived difficulty of the target. Changes in the percentage of more favorable outcomes can be linked to discrete developments in technology. By the end of 1999, the screening deck had increased to 200,000 compounds, but many assay formats were vulnerable to fluorescent interference. Chemotypes discovered during this period were often neither chemically tractable nor potent enough to warrant significant chemistry investment. From 1999 to 2003, the composition of the screening deck had been significantly enhanced, both

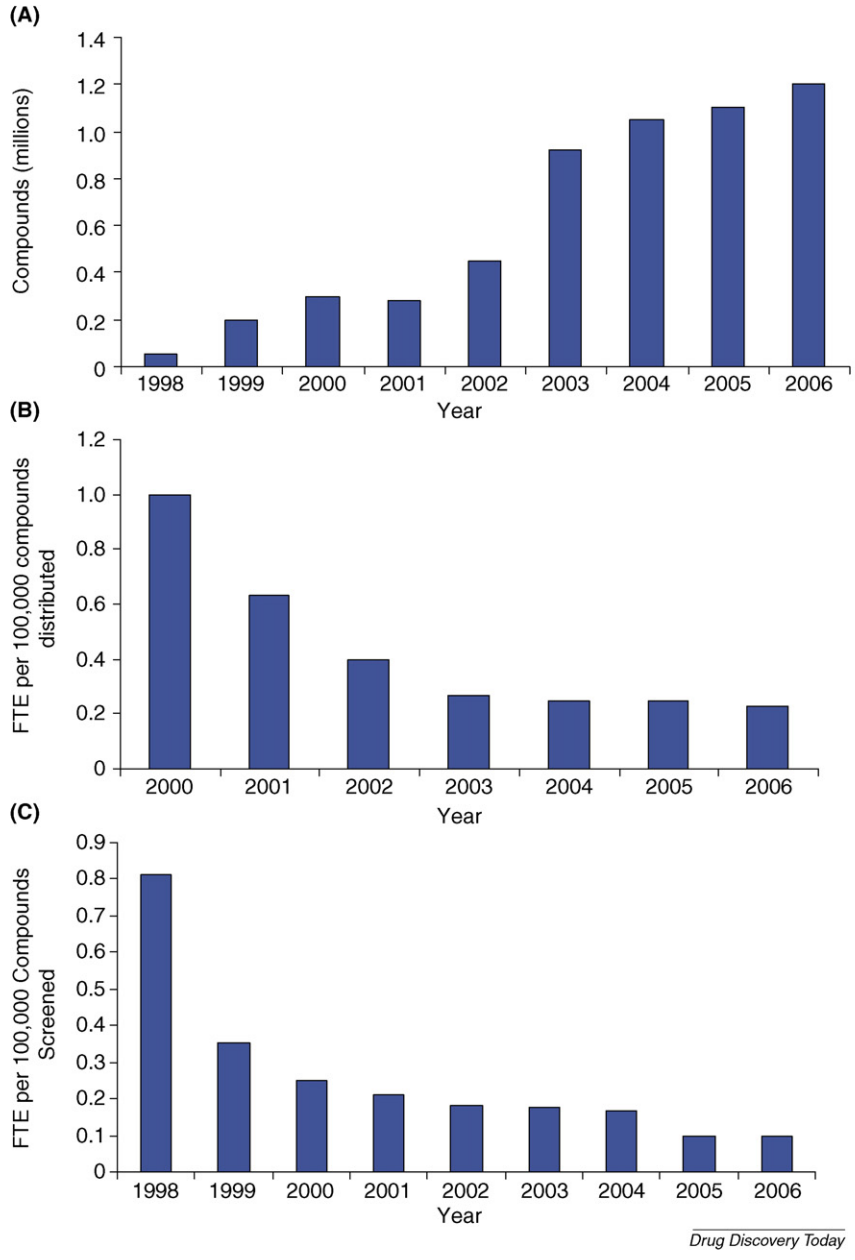

FIGURE 2

Efficiency metrics related to deck size and screening efficiency at BMS, 1998–2006. (A) Growth in size of the compound collection at BMS. (B) Manpower resource requirements for distribution of samples for all uses FTE = full time employee equivalent; data not available before 2000. (C) Manpower requirements for screen execution.

by filtering undesirable chemotypes and adding higher-quality acquisitions. Time taken to screen the larger compound deck remained unchanged as a result of automation, miniaturization, and shorter read times through imaging. These favorable trends were first reflected in an overall increase in utilization of HTS by drug discovery programs. By the end of 2005, 80% of all new drug discovery programs at BMS employed HTS as part of their drug discovery strategy compared to less than 40% in 1999: Secondly, the overall impact of screening approaches on drug discovery programs had significantly increased such that, by the end of 2006, enabling and significant contributions had grown from 10% to 65%. This has resulted in a number of programs progressing into the discovery pipeline that have benefited from screening leads and have the potential to progress to the clinic [30–33]. In fact, during the period 2002–2006 10% of the compounds in clinical development at BMS were positively impacted by screening approaches.

From the BMS perspective, the most important indicator of the enhanced impact of high-throughput screening can be found in its seamless integration into the drug discovery process. Across the industry, HTS groups have attempted to assess their successes and failures through conference presentations [34], surveys [35] and in

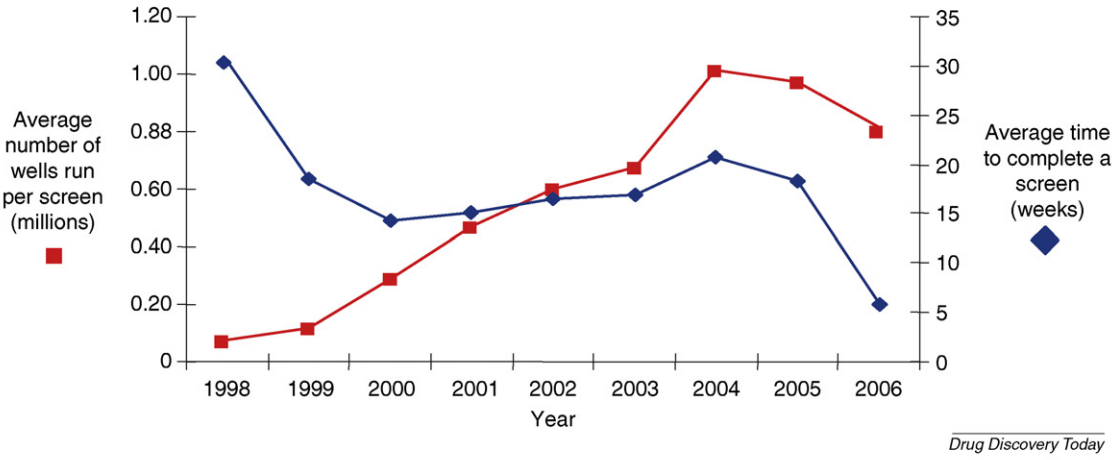

FIGURE 3

Average size of screening campaigns and average times for screen completion at BMS, 1998–2006.

crucial reviews [36,37]. From these sources, it appears that BMS has deck size and screening timeline metrics similar to most large pharmaceutical companies, and that our FTE efficiency and cost effectiveness compare favorably with our peers. A recent survey tracking responses from more than 45 HTS groups reported an average success rate of more than 50% for generating leads [38], with 0.104 clinical candidates and four-marketed drugs traceable to screening campaigns [39,40]. The over hyped promise of HTS, combinatorial chemistry and genomics in the late 1990s has given way to several key lessons. The quality and diversity of a screening deck seems to have a much bigger impact on lead discovery success than the size of the deck, while how compounds are stored and maintained can also have a crucial effect on success. Screening platforms and methodologies have improved through trial and error to the point where they are no longer a competitive advantage. Robust, flexible screening platforms are available to academic laboratories and large and small pharma firms. What seems to differentiate successful lead discovery organizations from less successful ones is their ability to seamlessly integrate and control the quality of the whole process including screening deck construction and maintenance, choosing the appropriate assay design for the target of choice, running flexible, reproducible HTS platforms and comprehensive compound profiling and annotation. A more parallel approach to lead generation, optimization and toxicity profiling appears to offer the best chance of consistently producing high quality lead series [41–43].

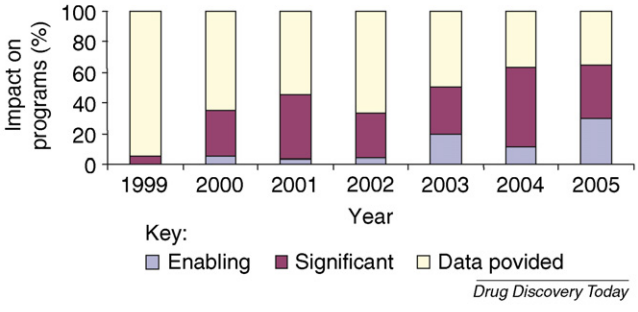

FIGURE 4

Year on year assessment of impact that high-throughput screening has had on drug discovery programs at BMS. Enabling contributions provided the structural basis for programs that were assigned full manpower support after management review. Significant contributions played a crucial role in informing structure activity relationships. 'Data provided' includes all other outcomes.

Lessons from the bleeding edge

The integrated technology infrastructure described above is the end result of a portfolio of technology investments that involved varying degrees of risk. Our portfolio also included three innovative screening approaches that provided ancillary benefits but ultimately failed to supplant our mainstream track-based screening platforms: first, a collaboration in 1997–2001 among BMS and several other industry partners focused on developing an Ultra-High-throughput Screening System (UHTSS) built around a high-density, low volume plate format supported by novel liquid transfer and plate handling systems. The system achieved proof of principle at high-throughput (500,000 wells/day) in our hands [44], but its proprietary FRET-based assay format limited its applicability to a narrow range of targets. The highly specialized support and maintenance requirements for UHTSS made the system much less cost-effective than the track-based systems, and it was ultimately decommissioned. Second, the Thermofluor® assay system [45], developed to measure changes in melting temperature of a solubilized protein caused by equilibrium binding of test compounds, also fell short of delivering its promise of screening targets of unknown function. The effort necessary to produce and characterize proteins proved to be just as costly and time-consuming as traditional *in vitro* assay design. It has, however, proven to be a powerful tool for characterizing novel gene products [46] and guiding protein purification. Finally, we investigated format-free screening [47], in which assay components are applied to a 'lawn'

of immobilizing matrix rather than dispensed into individual wells. However, 384- and 1536-well micro-titer plates represent a robust, well-supported technology platform that cannot be easily improved upon by format-free approaches. In our experience, the only area where a revolutionary approach has proved superior to incremental evolution has been low-volume acoustic dispensing. We believe that conventional syringe-base dispensing has reached the end of its evolutionary line, and acoustic dispensing is superior to competing techniques such as pin-tools or piezoelectric technology.

Conclusions

Judicious investment in key technologies operated by a highly trained and skilled staff has enabled BMS to gain maximum efficiency within lead discovery. A 24-fold increase in the number of compounds screened has been accompanied by a fivefold shortening of screening cycle times. Improvements in compound management infrastructure, increases in the size of the screening deck, and advances in screening technology have expanded our early discovery capacity and enhanced the quality of starting leads for new discovery programs. Combined with similar advances in liability profiling and lead evaluation, this has resulted in numerous examples of rapid progression of exploratory programs to full medicinal chemistry programs, and the generation of highly characterized development compounds with good potency and minimum liabilities. It is premature to assess the impact of these investments on new product approvals because clinical development is a multi-year process, but we believe that they will favorably influence overall success rates. Over the past eight years, a number of significant lessons have been learned about how to improve the lead discovery process and maximize your chances for success (Box 1). Technology investments have played a crucial role in allowing the lead discovery process at BMS to be significantly improved and more successful. We will continue to monitor the impact of these technology investments over time, evolve the platforms being used, and assess when these approaches have reached the end of their useful time span.

BOX 1

Lessons learned for a superior lead discovery process

1. Grow the screening deck to the optimal size for the organization's needs
2. Continuously improve deck quality and diversity through careful selection and filtering
3. Monitor and maintain sample integrity through environmental management, careful handling and proactive quality control
4. Apply assay technologies appropriate to the target type and as physiologically relevant as possible
5. Apply 'real-time' quality assurance through on line monitoring of screen performance
6. Annotate screening leads in multiple selectivity assays
7. Profile leads early for metabolic, toxic and pharmaceutical liabilities
8. Miniaturize assay volumes to minimize consumable and reagent expense
9. Design and maintain robust, reliable automation and informatics systems
10. Build and maintain a highly skilled, multidisciplinary lead discovery team
11. Integrate lead discovery technologies, processes and teams

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