Delivering the power of discovery in large pharmaceutical organizations

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Increasing the output from discovery is currently a major objective for the pharmaceutical industry aimed at reversing recent downward trends in productivity. Although significant attention has been focused on innovative assay and process technologies, these only address specific points in the discovery process. Little effort has been made to manage the multiple interconnected steps within discovery effectively. This manifests itself in low utilization rates of component elements and low expectations of delivery to any agreed timescale.

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▼ The application of collaborative planning techniques in the pharmaceutical industry has the potential to provide the next significant increase in discovery output. Collaborative planning tools have already been developed in other business sectors where process predictability and standardization are low, yet individual organizations are still held to account for timely delivery of output.

Driving change in the discovery process: a wholesale change or process evolution?

It is now generally accepted by even the most optimistic of pharmaceutical executives that the historic levels of performance within their organizations are not being sustained. Despite year-on-year increases in the R&D budget (>US$45 billion in 2001) the number of new active substances (NASs: genuinely novel substances as opposed to line extensions, re-formulations or approvals for off-label indications) has declined significantly in recent years, and has at-best levelled out (36 in 2001; Fig. 1). Evidence of this is beginning to be seen in the stock prices of the major organizations. Even in a general environment of depressed global stock markets, the value of pharmaceutical stocks has declined in real-terms over the past 18 months [1].

Big pharmaceutical companies have the expertise, resources and scale to take advantage of scientific and technological advances in biology and chemistry to generate new drug molecules entirely in house (and hence retain the full market value). However, unless large organizations are able to leverage their size advantage, they will not recoup the huge investments made in technology, staff and the organization as a whole.

This review outlines how these challenges have already been successfully addressed in other high-technology R&D-based industries faced with similar operating environments through the use of advanced collaboration techniques, and how such techniques can be applied to the drug discovery process. Although these approaches are applicable to the whole pharmaceutical process, we focus on the area of assay development and HTS, which is renowned for being unpredictable and automation intensive, requires reagents from multiple sources, has long lead-times, and, currently, has a high investment barrier for low utilization.

Transferring new approaches and technologies across industry sectors is usually difficult because of misconceptions surrounding their applicability and impact. We believe that implementing appropriately tailored integration and planning approaches to the industry will significantly increase productivity. It is important to note that this approach aims at leveraging the existing science and technology base. It is not aimed at reducing headcount or removing innovation (indeed, this is fundamental to the overall success of the industry). Although this review exemplifies a discrete part of the process, the approach can clearly be applied to the whole discovery process where more difficult obstacles exist in the search for chemical entities.

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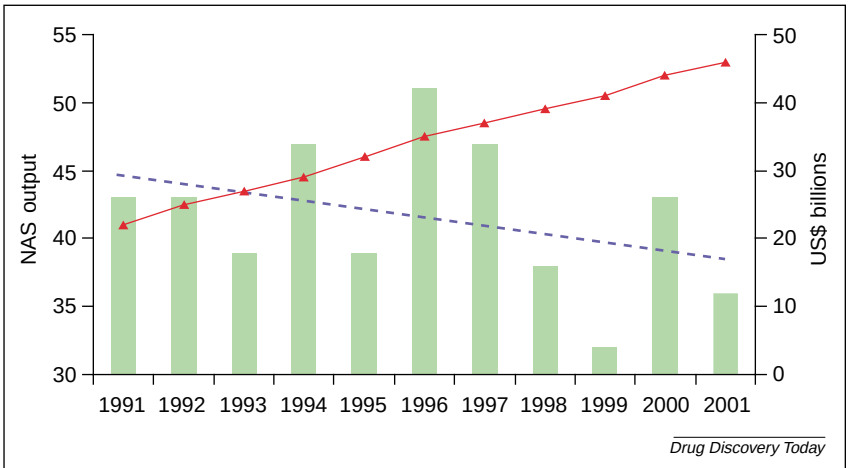

Figure 1. R&D productivity continues to decline at the industry level. New active substances (NAS) approved by the FDA (blue bars) are shown by year, with the average output indicated by the dotted line. The red line indicates investment ($US billions) by the industry.

Finally, examples from other industries using such techniques, and from changes in the pharmaceutical industry, demonstrate that the biggest challenges to successful implementation will be effective management of the human aspect.

High-throughput technologies: a diagnostic of the current productivity gap?

High-throughput screening has frequently been portrayed as being the frontline technology within pharmaceutical discovery, and, over the past decade, the industry has witnessed an apparently astronomical increase in the capabilities of its HTS groups [2,3]. Despite considerable progress in HTS functions within the industry, there is an inconsistency between HTS capabilities and the annual output of pharmaceutical lead identification (LI) groups (of which HTS is an integral part). Calculation of the typical mean screening throughput of installed screening systems in the industry reveals daily throughputs of between 2300 and 7400 results per system. This represents only 2–7% of the theoretical installed capacity (given the benchmark figure for installed capacity is 100,000 results per system per day) [4].

The explanation for the large discrepancy between installed HTS capacity and realized output is complex. It is unfair to blame the screening groups for simply not keeping their hardware platforms busier. In several cases, there is little backlog of work and the performance metrics of the group suggest that screens were run at a reasonable efficiency when a stable screen method and all the required components were available. Instead, the real issue with the performance of LI groups currently lies outside HTS. Addressing the overall productivity gap requires a holistic approach as, like most processes in discovery, HTS is critically dependent upon multiple inputs, without any one of which no activity can commence (Fig. 2).

The mounting external pressures on the pharmaceutical industry to maintain current shareholder value further exacerbate the problem of operation efficiency and predictability. Several major pharmaceutical companies have concluded that they need to increase the output of their discovery functions some 2–3-fold if they are to maintain their current profitability indices. This translates to a need to set-up some 100–150 LI campaigns per annum at current R&D attrition rates. Depending on the screening philosophy of the organization, each of these targets will be screened against a library of between 100,000 and 1 million compounds. There is debate about whether focused screening is a better approach than diversity screening for finding novel leads. However, for the supply groups, the demand involved in screening a diversity set of one million compounds is not much more than that required to screen a small focused set of 100,000 compounds.

Along with the increased productivity demands imposed by new HTS targets, additional discovery strategies also increase the pressure on operational efficiency. Many organizations recognize that the high attrition rates in preclinical and early clinical phases are a result of biometabolism or toxicological effects of the compound *in vivo* rather than a lack of efficacy at the primary target. As a result, several organizations are now addressing requirements for large-scale *in vitro* profiling of compounds before entry into preclinical phases. We believe that this shift in throughput, often termed the 'industrialization of discovery', can be achieved by applying lessons learned from other industries. Crucially, this approach must accompany initiatives that improve the overall risk and portfolio management in discovery as well as those that address the quality of the biology and its outputs. These two important elements are not covered in this review.

Adapting the existing model to deliver new challenges

Clearly, if the stated productivity targets are to be met, a means of increasing the effectiveness of discovery productivity must be identified that is also efficient in its ability to handle frequent change. Simply increasing the installed

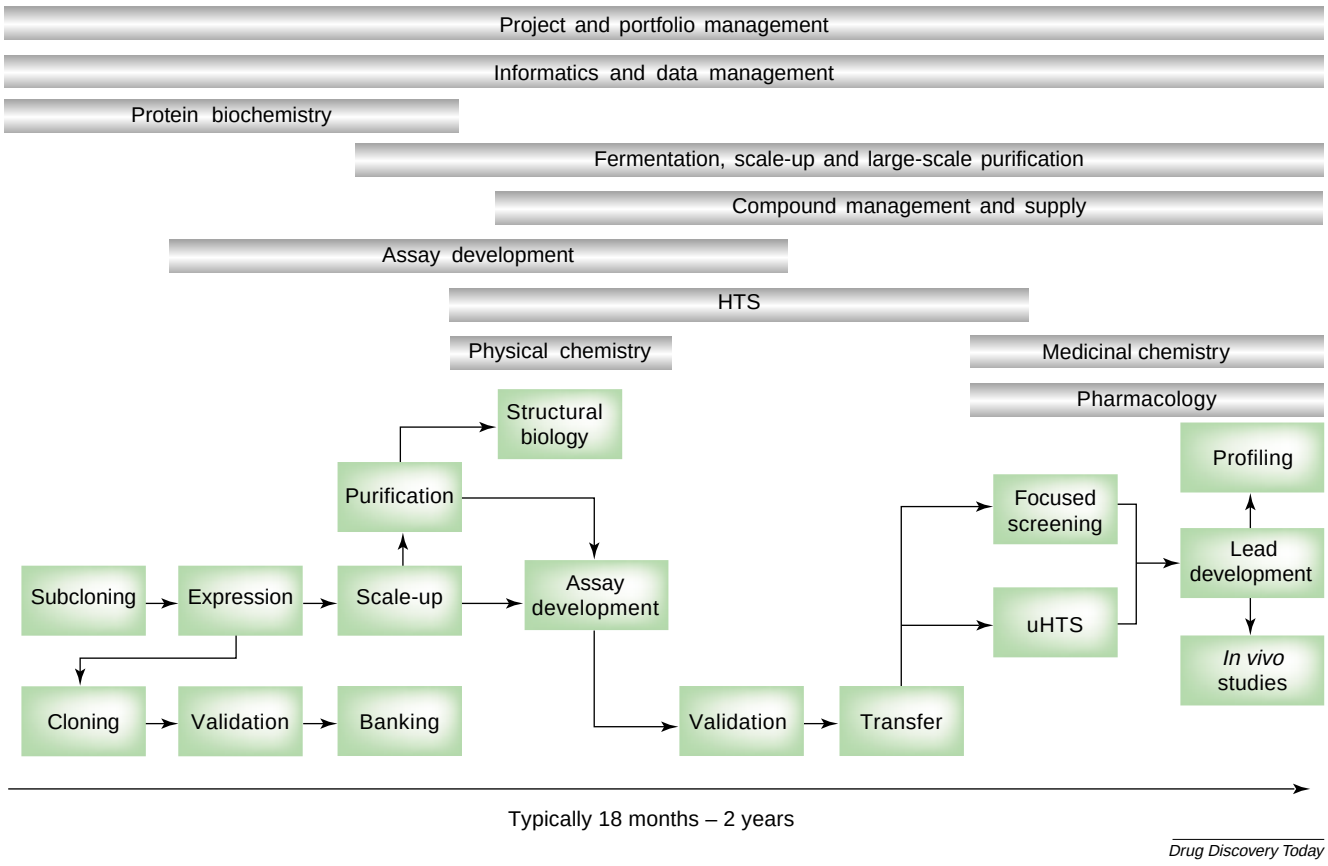

Figure 2. Process and organizational complexity in lead generation. The figure represents the various functions (grey bars) and process steps (blue boxes) typically involved in lead generation. In addition to the complexity represented here, large organizations are often geographically distributed by process and therapeutic area.

capacity of the facility 10-fold and expecting it to operate at a 5% utilization rate is not a desirable scenario for reasons of capital expenditure, facility space, headcount, and support costs. The solution is the integration of existing process and organization across function, discipline and geography; it is here that the challenge lies [5].

Unfortunately, the pharmaceutical industry is in danger of repeating the mistakes made in other industries in their attempts to industrialize. To date, there has been little attempt to coordinate investments against a high-level framework plan such that each new investment is seen as enhancing the overall capabilities of discovery. Discreet positioning of automation within the process does not ramp-up overall productivity without broader integration of process, organization and people.

In our experience, major technology investment decisions have been made within the narrow functional domains of individual groups, with the overall desire to improve point productivities in discrete areas. The key issue for the industry, therefore, will be how to manage its operation to enable the non-linear demands and the unpredictability of the underpinning activities. Simply assuming that scientific processes can be managed in a highly process-driven manner is not sufficient. The research process, in its nature, is unpredictable; the real issues are those of communication, proactive scheduling, and planning across the whole process chain rather than optimization of discrete local elements.

Planning in an environment characterized by uncertainty

Conventional methods used to plan research processes, such as spreadsheets, Microsoft (MS) Project, or semi-manual tracking databases, have become increasingly inadequate for the sophisticated needs of modern drug discovery. In the absence of anything better, scientists working with such tools in local geographical groups typically result in only a local optimization based on the scientific team and laboratory equipment; this has a detrimental effect on the overall throughput of the process.

Successful industrialization of the high-throughput discovery process must: (1) maintain the innovation and creativity of the discovery process; (2) increase productivity of lead discovery as an integrated process; (3) make effective use of global resources from a defined process (e.g. cloning to lead optimization); (4) optimize lead discovery process-throughput through integrated planning; (5) achieve and quantify value from investments and alliances; (6) reduce the unit cost of the process; and (7) develop a culture of collaboration across the global discovery organization.

Microsoft Excel and Microsoft Project cannot meet these objectives as they plan sequentially against required resources without checking constraints or modelling true dependencies. However, advanced planning and scheduling (APS) tools can now be adapted for use in discovery. These tools have proven capability in conventional operational supply chains and provide a higher level of sophistication. They ensure that all materials are available on time and in the correct quantity and quality to run each step of the process. For example, cell or protein production can be integrated with the replenishment of laboratory reagents and the dispensing of filled plates by automated liquid-handling systems. Flexibility and responsiveness are maintained using real results from the whole process enabling rapid re-planning in the inevitable event of changes to the original timeline. Therapeutic leaders are engaged by formalizing campaign planning against selected targets, and by dynamic feedback of campaign progression against original project timelines. Using dynamic modelling, APS tools can recognize and plan against actual constraints (e.g. availability of specialist assay platforms, IP constraints preventing screening of discrete receptor classes in certain countries, and local radioisotope limits). In addition, 'bottom-up' modelling reflects the real complexity of the process across functions and locations, accounting for scientific resources, automation and lab equipment (e.g. actual availability, skill type, and interdependency on other resources or materials). Data are collected from various sources (cross-functional and cross-geographical) to inform the plan, including collaborations with partners outside of the business, to link up with key suppliers (reagents and consumables) and collaborative researchers. This enables key suppliers to improve their planning cycles, and hence improve their relationship with the pharmaceutical customer. Such tools also provide a highly configurable reporting functionality to derive the business benefit from data being tracked within the planning system. In addition, certain scenarios can be simulated to support the decision-making process, to identify bottlenecks, or to model projections of future capacity before expensive capital equipment is ordered and commissioned.

It is important to understand that moving to a collaborative environment does not require expensive software development programs: the software to deliver this capability already exists. One of the greatest changes will be human-based, as industrialization requires compliance with planning process disciplines but not, crucially, standardization of scientific approach. Many creative environments reject these disciplines, as they are perceived as enforcing constricting behaviours on an environment that is, in its nature, unpredictable and non-standardized. Any planning model must be run against a predictable process backbone without compromising creativity. In essence, this means identifying those parts of the process that can be described as occurring for any drug discovery project to support consistent planning. Realizing this balancing act in the working day of the scientist will be the crucial success factor in bringing collaborative processes and planning system disciplines into our model of a high-productivity R&D environment.

What is collaborative planning?

Collaborative planning offers much to the segmented, complex supply pathways that define drug discovery. It has been proven in other R&D-based industries with long lead-times, high investment, and high-product liability, such as the computer or aerospace industries, which have pioneered collaborative industrial thinking within their organizations. The change to collaborative transparency is hard, as it brings with it cultural and control issues, as well as the need to question the current operating modes of the overall business process [6–8].

The aim is to move towards becoming a more performance-driven organization (where performance is defined as output of high-quality leads with sufficient information to enable effective decision-making for progression into clinical phases).

We believe that the opportunity to leap directly into a performance-driven environment is real, and that the tools to assist in the strive for dramatic increases in productivity are now available.

Successfully engineering a transition swiftly through to a throughput philosophy can be achieved through collaborative planning. This horizontally integrated approach to managing a business has proven to be dramatically successful in many other sectors of high technology, R&D-intensive industry. Reports from cross-industry manufacturing suggest that collaborative planning yields an improvement in service levels between organizational

units (and external customers) of up to 100%, improved business interaction with business partners, and a reduction in forecast error leading to stabilization of planning by 20–30% [9]. Furthermore, according to modelling work by leading industry analysts, automotive manufacturers estimate a reduction of 21% on project costs, and the slashing of project timelines using collaborative planning during product development [10].

The key to collaboration is ensuring that all parts of a connected enterprise are working together on the same plan to ensure a joined-up series of scientific activity (Fig. 2). These plans can work through a planning hierarchy and be orientated to meet certain stated financial or corporate goals for a business. Once such an environment is in place, the process of day-by-day execution of the plan is smoother, as teams are managing by exception against agreed expectations. It is very important that the plans are set cooperatively against known capabilities. These statements of capacity are typically part of a strategic resource management approach and have to be more sophisticated than extrapolation of total campaigns from previous years. To be of value, they should be based on an accurate understanding of the resource cost (time and headcount) of prosecuting specific LI campaigns. Portfolios will change with different gene target classes and different diseases over time, and having an accurate view of capacity against demand will support both planning and budgetary procedures. Initially, these statements of capacity and resource cost are derived from an accurate analysis of historical performance by process stage and campaign type (e.g. gene family and disease class). Once the approach has been implemented, it is important to record performance accurately to refine the capacity model continuously. By doing so, the accuracy of the model improves but also changes to reflect variances in resource cost owing to increased experience with target classes or new platform technologies. Furthermore, by measuring output, it is possible to relate any problems to a fixed root cause and communicate the effects up- and down-stream in the physical flow of activity to ensure that everyone has an opportunity to identify corrective action.

But how is it possible to enact such collaboration? A typical business is complex; it invokes many hundreds or thousands of resources and materials and complex non-linear processes. Many rules and options govern its operations and there are many interactions that need to be considered from one end of the process to the other. The key is to focus on what are the major process components and to direct attention to those areas first, thereby simplifying the problem around the key constraints in the overall process, and then ensuring that all other areas are synchronized to the constraint plans.

The most important first step is to define clearly the goals of the overall process. The goals of the subcomponents of the process can then be developed – this is already common practice in the industry. Without a clearly stated goal it is impossible to engineer a plan for the business. In the absence of such stated goals, management will create their own, and there is no guarantee that all will be working together to yield optimal results for the global business.

Second, the characteristics and constraints of the process are modelled such that all elements of the chain are clearly defined as a foundation on which to collaborate. Once this is completed, the model is inserted into the appropriate tool in which to develop integrated plans. It is then possible to analyse productivity capability using a real quantitative tool and model.

Third, operational measures that can be monitored or tracked on a daily, weekly, monthly or quarterly basis need to be identified that will enable management to relate process performance back to corporate objectives.

Therefore, an effective collaborative plan must be positioned to perform collectively against a common goal. It must tie together the strategic, tactical and operational plans so that each relates completely to the other. It must also be capable of real-time exchange of information to support the execution of the plan, enabling rapid reaction, re-planning and reporting such that all the functions and groups involved have a real-time view of the current status of the project.

Collaboration in practice: application to drug discovery

For the logical framework described previously to work, it is absolutely essential that the plans address reality. One of the real technological barriers to implementation for businesses over the years has been the inability to model the individual processes that make up a chain of activities. In recent years, supply-chain management companies have made dramatic breakthroughs in this area, enabling real linkage between strategy, tactics and operations. This is now well-positioned in support of other processes that are less manufacturing orientated, such as design, development, maintenance and services.

One requirement is to ensure that the constraints within the processes are understood at all levels of planning and scheduling, and, should any issues be encountered affecting the performance of these constraints, that it is effectively communicated around the system. Without this, it is impossible to keep the plans up-to-date.

The modelling must be capable of understanding the linkage between capacity and materials required at any activity, and must also carry the rules that govern the manner in which management wish to run their operations. As mentioned previously, these APS tools have significantly enhanced functions over those used traditionally within discovery. At their core, they use real-time data and a true model of the entire process.

Activity level modelling at the laboratory bench level captures the process for various campaign types. Logical finite management monitors equipment capacity and materials in any process, such as reagents and proteins, or cells that recognize a sequence of events. For example, a cell line cannot exist until the cells have been cloned, and the cells cannot be cloned until the transfected cell lines have been validated, and so on. The constraint-based focus centres on a detailed understanding of the capability of each step by modelling the technical and scientific human resources. For example, certain assays require specific platforms and detection systems, and might require specific personnel to run them. Alert-based reactive mechanisms are based on implicit process regulations that alert users to exceptions or delays that might impact a scheduled downstream process step, such as the contamination of fermentation run. These can also be linked with inventory systems that automatically monitor reagent use, triggering, for example, an alert in scale-up and purification to expect an imminent request, thereby enabling personnel to proactively prepare or re-schedule. In addition, interactive planning and communication to the various workgroups in the chain, based on the up-to-date master campaign plan, enables, for example, the preparation of reagents or technology platforms, or the ordering of reagents from key suppliers. Full monitoring and analytical capabilities enable performance measurements to be managed, facilitating an understanding of process performance for further optimization. The model also has open communication pathways to legacy and external systems, as it is unable to function properly without being integrated into existing information architecture. Finally, flexibility in design enables the tool to be (re)configured to the particular needs of the new technology and the constraints of an evolving discovery process.

Working in a collaborative environment

Figure 3 illustrates how such a collaborative process would work in reality within the lead discovery environment.

Stage 1

Working with the therapeutic leaders, a forecast of expected screening campaigns is agreed upon, based on target identification programmes and discovery goals. A forecast such as this is only truly effective if it covers 2–3 years. Initially, this appears difficult, but many businesses manage this by changing the level of the forecast over different 'horizons' against which a 'frozen' (short horizon of 2–4 weeks, high certainty, difficult to change), 'slush' (medium horizon of 1–4 months, moderate certainty, can be changed) or 'liquid' (long horizon of 6-24 months, low certainty, certain to change) plan can be set. These horizons are set based on the constraints of the process, that is, how long it takes to carry out a single type of campaign, and the quality of forecast that the team agreeing the demand can predict (e.g. how far ahead they can be certain as to the exact target type they wish to investigate). New campaigns are added to the system as they are approved.

Stage 2

Using these forecasts, a constrained master plan can be set by placing the demand of the lead development process on the model. This model will cascade the demand from lead optimization back up through screening, protein and cell production, and gene expression and assay development, at an aggregated level. The model will understand the constraints in terms of equipment type that can run certain assays, scientific resource (e.g. technical personnel available), reagent availability (in terms of stock and consumption), lead-time to carry out gene expression, cell production and protein purification, and the overall workload of existing campaigns. To give a more realistic process model, these lead times are based on data for specific assay types, gene families or pharmacophores rather than just a general campaign time. This master plan sets the high-level commitment, in terms of dates and volumes, against the forecast. If there is a lack of capacity to meet the forecast campaigns then the model will highlight options to re-plan, or defer and/or change forecasts. Obviously, this feeds real data into a decision-making process that discovery management teams would carry out monthly or quarterly. The campaign master plan will usually cover the foreseeable medium-term horizon of about 18 months.

Stage 3a–3c

With the campaign master plan agreed, the next level of planning can begin with departments such as assay development and protein and/or cell production developing a monthly plan for their teams and laboratory resources. These 3–4 month site plans will be set against the overall campaign master so that commitments can be made to support subsequent steps in the process. This plan enables local optimization before the short-term schedule is fixed.

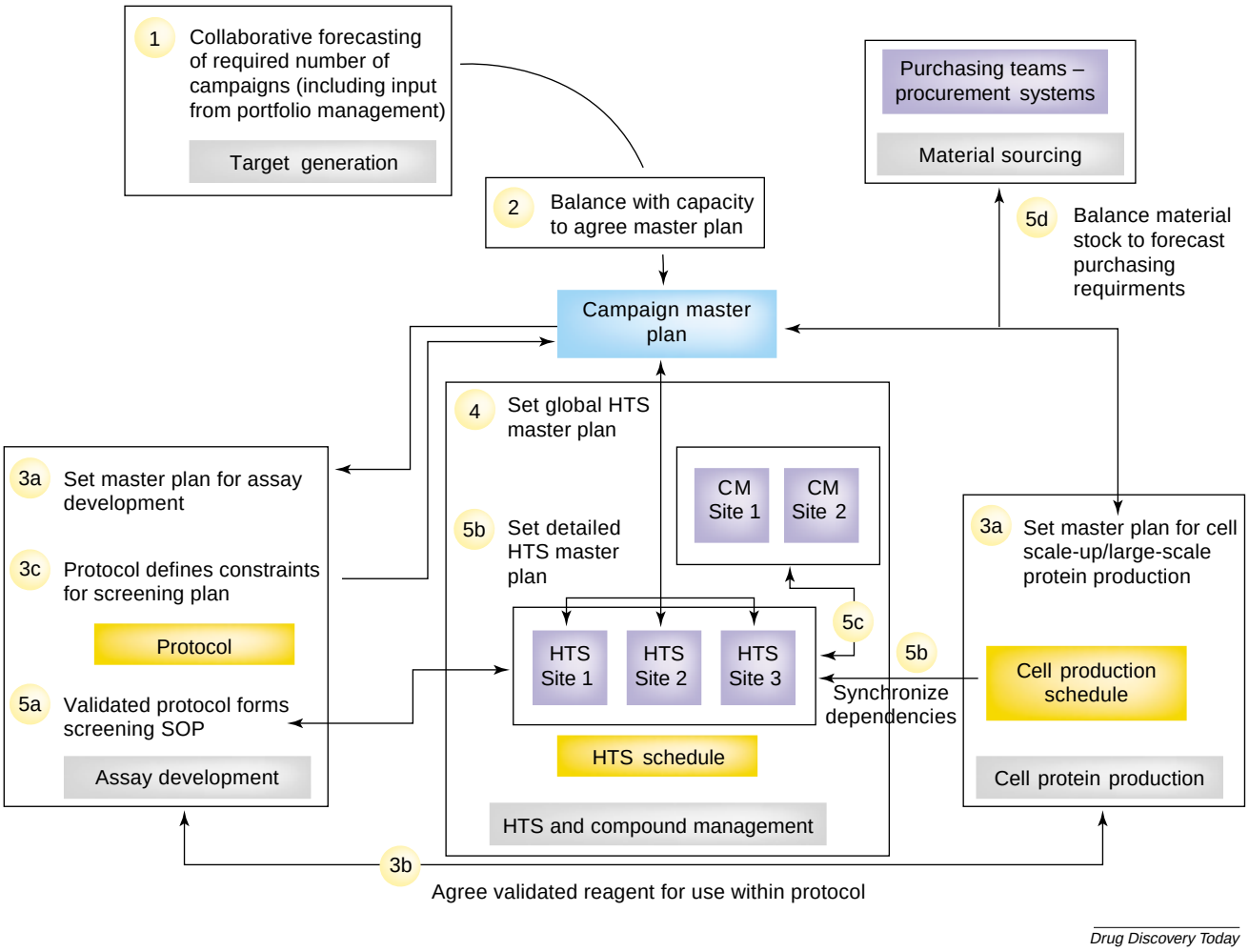

Figure 3. The collaborative planning process. The figure shows the collaborative planning process as it would work for one part of the lead identification process, covering identification of a validated target through to identification of a post-HTS hit. This approach would normally be extended to include the downstream activities around profiling, lead development and lead optimization. Numbers 1–5d refer to stages detailed in the main text. Abbreviations: CM, compound management; SOP, standard operating protocol.

Stage 4

With the upstream part of the process in place, the plan for each of the sites can then be set against the expected availability dates for protein, cells and adapted assays. Again, this requires site-by-site optimization to local equipment, skills and available resources.

Stage 5a–5d

The site plans will set the high-level week-by-week commitments but these have to be realized through finite scheduling of each operation. This schedule is at the activity level and will cover the timeframe of a day or less. The schedule is set and controlled locally and works with the locally known constraints and resources to ensure that the site plan is met. The schedules are sequenced with all the necessary inputs and outputs because all are interrelated through the higher level plans. This integrated sequence ensures optimal speed for the campaign as it progresses downstream through the lead development process by managing known bottlenecks, such as gene expression or protein purification, and by preventing stoppages owing to lack of material. The schedule also uses a 'materials requirement planning' functionality to drive the delivery of reagents and consumables to a screening station, as well to manage the inventory in terms of stock and sourcing.

It is this flexible and inclusive approach to planning that makes it genuinely collaborative. Any approach that is based on central command and control will not work in an innovative R&D-based environment.

Box 1. The evolution of collaborative planning for drug discovery

The evolution of collaborative planning has resulted in its development and implementation such that its approach is ideal for R&D and service-based processes. Early methodology developed for manufacturing focused on an integrated seamless supply chain, and functional excellence to remove cost and improve service levels. These approaches have been successfully adapted for the more service-based elements of HTS, such as compound management, where tight control of supply and inventory has been key. Over the past five years, these approaches have been developed to adaptive techniques aimed at improving the productivity of global organizations by providing a real-time method of balancing demand with resource requirements across the whole globally integrated process.

Features of an integrative process

- Seamless supply chain
- Functional excellence
- Decreased cost
- Increased service
- Increased throughput
- Effective compound management
- Optimization of protein and/or cell supply at single sites

Features of an adaptive process

- Collaborative (real-time) flexible operations
- Improved global performance
- Dynamic methods; balances demand versus resource versus strategy
- Planning linked to execution
- Global linking of the whole lead identification process
- Delivers broader organizational goals cost effectively
- Responds to inevitable uncertainty

What value will the business get from using the collaborative model?

We have suggested that there is a need to optimize current processes to deliver the demanding goals being set for discovery organizations; the way to achieve this is through the implementation of collaborative planning approaches. Once an organization implements such an approach they will see benefits in several areas.

Immediate advantages will be seen in managing productivity through the efficient use of existing screening capacity, and the flexible and increased use of equipment (ending the ring-fencing of equipment for certain campaigns).

Planning will increase overall control by: (1) improving the level of collaborative buy-in to campaign commitments through quality global planning; (2) use of a credible method for realistic and frequent planning; (3) increased flexibility from other planning systems by integrating activity across the entire process; (4) gaining reliability (by increased adherence of process to plan); and (5) providing an effective tool for forward-planning against changing priorities and changing portfolio.

Understanding the effect of demands placed on the functional teams in the process will be increased by: (1) responsiveness to the demands placed by having the confidence of a model that accurately forecasts capacity at a detailed level, and one that can reflect changes over time (e.g. greater experience with an assay format); (2) catalysing the development of methods to deal with internal and external customers; and (3) formalizing the forecasting processes with therapeutic leaders to gain upfront agreement to needs across all therapeutic areas.

A better understanding of global organization and culture will be developed by: (1) moving away from the 'master craftsman' culture; (2) inculcating an industrialized culture that separates scientific activity from throughput-driven activity; and (3) moving from a local physical team atmosphere to a virtual collaborative culture.

Globalized planning will become more efficient through: (1) driving plans across all global facilities into one integrated sequence, and clarifying joint priorities; (2) realizing visibility through clear metrics; and (3) deepening collaboration across sub-processes where visibility encourages trust rather than exposure to sanction.

Better management of the suppliers of reagents, consumables and other materials will: (1) ensure delivery on-time and to agreed levels to prevent stoppages; (2) provide management of radioactive substances and other high-value perishables; (3) achieve cost control of stocks and optimization of pricing through strategic sourcing; (4) manage supplier capacities (multiple sources and metrics); and (5) ensure quality control of supplies received.

Finally, increases in throughput will be better managed by: (1) defining clear hardware requirements for high-throughput equipment; (2) investing in and justifying long-term sourcing of assets; (3) commitment to the business plan; and (4) setting realistic team objectives against realistic capacities.

Concluding remarks

Applying techniques from manufacturing, where the product is the output and the data merely a supporting side-product, to a discovery process, where the product is consumed to deliver the output in the form of data, is indeed a novel idea. However, collaborative planning has itself changed from early approaches developed to deliver seamless supply chains in the manufacturing industry (see Box 1). The past few years have witnessed the development and adoption of these approaches in non-pharmaceutical R&D and service-based organizations where the delivery of

an integrated process and organization will improve global performance. In these industries, the argument for collaboration is supported by evidence that integration across global diverse functions improves learning, quality, speed of throughput, and ultimately productivity. In summary, industrialization centres on having a clear technology strategy that targets investment in technology platforms, supporting productivity without compromising innovation. It follows clearly defined pathways (without limiting the routes for creativity), where high-quality reagents and materials are used (to ensure global consistency of data outputs), and where common processes are followed (to generate consistent results). It is still completely dependent on good basic science to produce validated drugable targets in relevant assay formats, and to produce high-quality lead candidates from initial drug-like hits. However, if pharmaceutical discovery implements such approaches in an appropriate way, the vision of a genuinely networked lead discovery organization is attainable, and the productivity gains that have been witnessed in other industries will be achieved.

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