The worldwide pharmaceutical industry faces a crisis of rising research expenditures and declining rates of introduction of new medicines. Much attention has been focused on reducing costs and improving the efficiency of clinical trials, the longest and most expensive phase of drug development. However, increasing the value of the upstream drug discovery process may yield a significant benefit by increasing the likelihood of success of drug candidates. In simple terms, the product of drug discovery is a novel chemical compound capable of modulating a disease target with appropriate efficacy and selectivity, intended for delivery to patients after clinical development and regulatory approval. A more useful view of the process recognises that knowledge is the true product of the process. Every candidate to be advanced must be accompanied by a thorough understanding of the role of the molecular target in the disease, and a complete characterisation of the compound for efficacy and safety in a wide range of assays and relevant models of disease. Furthermore, the rate at which knowledge about a new drug class accumulates during the discovery phase directly affects the ability of the discovery team to optimise the structure and properties of the final candidate and thereby increase its chances of clinical success. The goal of this article will be to show that improving the process by which leads are optimised during drug discovery can be as important as the underlying science, and that the means for accomplishing this improvement can be found in the methodology known as lean thinking.

**Lead optimisation**

Initiation of a new drug discovery programme (Figure 1) begins with target validation and lead discovery, resulting in a therapeutic hypothesis that links a molecular target to a disease process and a chemical lead with some level of activity against the target. Both the degree of validation of the hypothesis and the suitability of the early lead may vary widely. Lead optimisation begins with an assessment of the disparity between the properties of the early lead and the requirements for efficacy,
selectivity and safety of the desired candidate – creating a pull of demand that is met by design and synthesis of new compounds that will deliver improved properties. Specification of exact chemical structures is followed by conception and execution of a synthetic route, then purification and characterisation of the resulting substance. New compounds are evaluated in a panel of biological assays chosen to elucidate the structure/activity- and structure-liability relationships (SAR and SLR) pertinent to the programme’s therapeutic hypothesis. Interpretation of these results augments the existing knowledge product, and the next iteration cycle begins. Each cycle of design, synthesis and evaluation of novel compounds adds an increment of knowledge that is utilised by the programme team in subsequent cycles, as well as by the development team downstream. Successive cycles continue until the teams decide that the target profile of properties for the lead compound warrants its progression into development. Most contemporary programmes are somewhat more complex than this simple model. Multiple lead series that differ in chemical structure are generally carried forward in parallel. The target activity profile of the drug candidate, including binding affinity, functional efficacy, selectivity versus related gene-family targets, and other attributes often cannot be specified until initial determinations of pharmacodynamic activity and pharmacokinetic properties of early leads have been assessed.

Lean thinking

Lean thinking teaches that a business will succeed by its ability to deliver value to its customer. By understanding the value of its product from the customer’s perspective, the business can ensure that every unit of resource expended in delivering its product yields maximum value to the customer. Every step in the entire path from raw materials to finished product – the value stream – is evaluated for its contribution to value. Steps that consume time and resource, but add no value are eliminated or minimised, and the remaining steps are linked so that the process flows in response to the pull of customer demand. By transforming a process through lean thinking, the business can supply the customer with a higher-value product that will command a higher price, but which has cost no more to make. The perfect process – delivery of value with no resources wasted – is acknowledged to be unattainable, but serves as a guide for continuous improvement of the process.

The antecedents of lean thinking can be found in early history, in the first examples of continuous manufacture, and in the advent of mass production.
at Ford Motor Company. The Toyota Production System has been the determining factor that led to Toyota’s current dominance of the automobile industry during a period when other corporations are in decline. ‘Just in time’ inventory and empowerment of workers to identify and correct assembly-line errors are examples of lean-inspired innovations that reduce cost and enhance value. In the decade following the popularisation of lean thinking by Womack and Jones, the method has penetrated all areas of manufacturing and been applied to processes as diverse as the filing of insurance forms, delivery of nursing care and the forensic investigation of crimes.

**Elements of value**

In manufacturing, the cost of producing a product and the price a customer will pay for it form the basis for measuring value. In contrast, the value of the knowledge product of drug discovery is not easily measured in objective terms. I will describe an approach to defining and measuring value in drug discovery that has proven to be an effective tool for analysing performance according to the principles of lean thinking. Regardless of the complexity of a drug discovery programme or the nature of the target, the lead optimisation process includes several common elements of value:

- **Scientific relevance:** Knowledge generated by a drug discovery programme arises from the formulation and testing of hypotheses that are relevant to the overall therapeutic objective. Compound design should reflect all pertinent learning from medicinal chemistry. Computational methods, QSAR analyses and structure-based design should be based on sound physicochemical principles. Assays chosen for compound evaluation should be strongly validated according to the most complete understanding of the basic biology of the disease area.
- **Capability:** All of the data generated in the programme must be of sufficiently high quality to engender confidence in its use. Novel chemical compounds must be properly characterised with respect to structural identity and purity. Assay results must precisely and accurately reflect whatever biological property – receptor binding, enzyme inhibition, functional activation, etc – they are intended to measure. Assays must deliver results that facilitate a comprehensive understanding of SAR and SLR over the entire lifetime of the programme. Pharmacokinetic and pharmacodynamic experiments in animals should be conducted in appropriate species and be capable of predicting clinical performance to the extent that scientific understanding permits.
- **Timeliness:** The time required to complete each knowledge-generating step in lead optimisation affects not only the overall duration of the programme, but also the degree to which new information is utilised in successive iteration cycles. In most programmes, design and synthesis of multiple leads and structural variants is carried on simultaneously. Any delay in characterisation of compounds limits the programme’s ability to utilise all of the SAR/SLR knowledge generated in previous iteration cycles.
- **Completeness:** Each of the thousands of compounds synthesised in a typical lead optimisation programme may contribute only a tiny increment of new information to the SAR/SLR profile for the programme. Compounds must be characterised as completely as possible to ensure that no important relationships are overlooked.
- **Efficiency:** The knowledge needed to advance a new therapeutic hypothesis includes basic biological research and proof-of-concept experiments beyond what is generated in lead optimisation. Therefore, compound synthesis and biological testing must be accomplished at the lowest possible resource cost. Routine SAR/SLR assays must not encroach on the resources needed to perform additional experiments to test the therapeutic hypothesis.

Thus, a process that provides the greatest amount of high-quality information about a drug class as early and as completely as possible will deliver the greatest value to its customers – the discovery and development programme teams –
enabling them to select a candidate with the greatest possible likelihood of success in clinical trials.

**Event-based analysis: objective measurement of performance**

The actual performance of the lead optimisation process for a drug discovery programme can be studied by an approach known as event-based analysis. In this method, the progression of each cycle of optimisation can be visualised for the entire programme history. The pertinent process information needed for this approach, such as dates and times when individual compounds were synthesised and evaluated in programme assays, can be readily found alongside the scientific content in the chemical/biological databases maintained by nearly all discovery organisations. Figure 2 shows a hypothetical example illustrating characteristics typical of most discovery programmes. The inset for Figure 2 shows the chronology for a single compound, in which each of the events depicted in Figure 1 are represented by a specific plot symbol in the timeline. Stacking the individual timelines for all programme compounds leads to the programme event plot shown in Figure 2.

One can readily discern that the synthesis of new compounds in the programme takes place at a fairly constant rate, but that most assays produce batches of results at regular intervals. The time required to characterise a compound completely greatly exceeds the time from synthesis of one compound to the next, and the extent to which individual compounds are characterised varies widely.

The power of event-based programme analysis can readily be used to inform programme management decisions in accordance with lean thinking principles. The rate of synthesis of new compounds determines the pace at which a discovery programme will advance, since it is only the availability of new compounds with improved properties that will allow the programme to reach its goal. Therefore, increasing the rate of synthesis through application of additional chemistry manpower resource is a common stratagem used to accelerate a discovery programme. However, increasing the synthesis rate in the absence of any change in the overall cycle time for full biological evaluation of a single compound means that the design of the additional compounds will be unable to benefit from knowledge gained in the most recent iteration cycles. In contrast, shortening the cycle time for biological evaluation of a compound means that a greater proportion of newly-synthesised compounds will be designed using up-to-date knowledge. Thus, this lean-based process change, which should be achievable with no additional resource cost, might lead to a better outcome than the costly addition of chemistry resource.
Mapping processes and enhancing value

Figure 3 shows a schematic diagram for the flow of compounds, materials and information that leads to the generation of information in a drug discovery programme. The diagram – known in lean thinking as a value stream map6 – is the starting point for identifying opportunities for enhancing value through process changes. The map is compiled by direct observation of day-to-day operations and annotated with information on the time and distance intervals between steps, the inventories of compounds, samples, or raw data that accumulate between steps, and the resources consumed in each operation. Both event-based analysis and value-stream mapping were utilised in a recent study of 40 drug discovery programmes at Bristol-Myers Squibb7. In general, while primary assay data was being reported at a rate that kept pace with novel compound synthesis, the performance of additional assays needed for complete elucidation of SAR/SLR lagged behind the rate of synthesis in both timeliness and completeness. Deeper analysis of assay practices showed that programme-specific assays were generally carried out at relatively infrequent intervals in a large number of laboratories, using a wide variety of technology platforms with no consistent utilisation of automation. Processes for distributing compounds and reporting results for each assay class included many redundant steps. The transformation of these processes began with the transfer of responsibility for most programme-specific assays into federated ‘Lead Evaluation’ laboratories manned by assay specialists. The greatest gains in performance were realised by simplifying compound distribution and assay plate preparation; consolidating assays on to proven technology platforms similar to those utilised in high-throughput screening; and standardising data acquisition, analysis and reporting hardware and software. These changes led to significant enhancements in value in all of the categories described above. The broad application of these changes across all programmes will provide a useful test of the benefits of lean thinking independent of the specific circumstances of individual programmes and therapeutic areas.

Is drug discovery ready for lean thinking?

The application of lean thinking to drug discovery will be a powerful complement to other approaches to improving industry productivity. DiMasi8 has argued that an increase in the success rate of compounds entering clinical trials from the currently observed 1 in 5 ratio to 1 in 3 will lower the total capitalised cost of each NCE by $220 million. Lean thinking in discovery will enhance development success by building a stronger knowledge base for every advancing candidate. Resources freed from activities that add no value can be used to broaden compound characterisation and exploit new scientific understanding to refine a programme’s disease hypothesis. Improved data quality – ‘getting it right the first time’ – will minimise rework and the cost of following incorrect information. Finally, every cycle of new compound design and synthesis will benefit from more timely and complete compound characterisation. The programme team will be able to deliver a superior candidate for development in the same or shorter time, and the final candidate will have a greater chance of succeeding in clinical trials. Evidence from early adapters shows that scientists committed to excellence in their quest for new medicines respond favourably to lean thinking’s emphasis on quality and value. Drug discovery is indeed ready for lean thinking.

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Dr Edward W. Petrillo retired from Bristol-Myers Squibb after a 31-year career. He invented the marketed antihypersensitive fosinopril, oversaw the advancement of several other compounds towards clinical trials, and led the development of many significant innovations in combinatorial chemistry, chemoinformatics, compound management and HTS. Dr Petrillo also pioneered the application of lean thinking to drug discovery and introduced event-based programme analysis for tracking process optimisation. He is currently head of Discovery Performance Strategies LLC.