Until recently, Cantor assumed that his life as a researcher would belong to the academic 'ivory tower' only. Now, however, he believes that the modern biotechnology industry could be a more favorable environment for the present-day life scientist. Accordingly, in 1998 Cantor joined Sequenom (http://www.sequenom.com), a German–US biotech startup company where he is involved in industrial genomics developing automated MS systems for high-throughput SNP analysis.

Acting as the Chief Scientific Officer at Sequenom, Charles Cantor is currently on a sabbatical from Boston University (BU). Yet, at his 60, Cantor is enthusiastically and concurrently hitting two targets: industry and academia. He remains active in the Human Genome Project through membership in a number of the project's advisory committees and review boards, and his Boston research laboratory continues to be active, and Cantor himself works there frequently during his visits to Boston.

Cantor's current research interests lie in molecular genetics and pharmacogenomics, genetic and protein engineering, and nanoengineering and microrobotics. These include the development of new robust methods for DNA sequencing and PCR analysis, the design of bacterial strains suitable for environmental detoxification, making detectors capable of recognizing specific single molecules, and construction of synthetic gene networks.

Charles once said that his dream is to make enough money from current business to spend afterward on doing what he likes most – learning about the origin, evolution and nature of life. On the occasion of Charles's diamond anniversary, let us wish him good luck in this dream!

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The dilemma of process development

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Process development helps get drugs to market faster, and is therefore crucial for company success. Although not every candidate makes it to market, they all consume process development resources. Where should development resources be deployed to maximize output of the drug pipeline: on the late-stage candidates nearing the market, on the most promising candidates, or on every candidate? In the face of a high clinical trials attrition rate, drug developers must adopt strategies that resolve the dilemma of process development.

The dilemma of process development

Most drug candidates never reach the market. Only 7–28% (depending on therapeutic class) of new molecular entities that start on the path to commercialization are expected to become products [1]. The high attrition rates of drugs under development, coupled with severe time pressures, confront process research and development groups with a dilemma. Although process development resources must be used to make clinical supplies under tough deadlines, the developer does not want to delay the approval of potential blockbusters in other programs by working on the commercialization of dead-ends.

The new compounds being brought to market are more complex and difficult to manufacture, and yet the time period of late-stage development has been seriously compressed in the past ten years. This is because of changes in regulatory requirements and the need of the pharmaceutical industry to develop better drugs at a faster pace to remain competitive and satisfy growth projections [2]. The commercialization effort for each drug candidate is an enormous scientific and technical undertaking, in the clinic, the laboratory and the factory. Establishing a supply chain, and the necessary manufacturing procedures, to make a potential new drug is part of the commercialization process and an important part of the drug regulatory approval process. Process development is commonly viewed as an activity that saves costs and capital in manufacturing

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– an important activity, but perhaps not vital. A well considered and executed process development program also gets drugs to market faster, increasing revenues and contributing to the success of a company [2].

Drug synthesis during drug development

At the earliest stage of drug evaluation, pre-clinical toxicology studies require only a few hundred grams of the compound. It is not unreasonable, usually, to expect a competent laboratory group to prepare the material for these tests using tedious and unproductive methods. However, this can cause a serious backlog if many projects in the pipeline are inefficient. Recent commentary in this journal recommended early involvement of process development chemists, even as early as the discovery stages [3]. Process chemists can contribute significantly to an early route, helping to cut time out of the discovery and early development stages. Those with process insight might be expected to render a judgment on this one aspect of the 'developability' of compounds and influence the selection of candidates at the very start of the development cycle [4].

In Phase I trials, the required quantity of active pharmaceutical ingredient (API) is normally 1–10 kg. At this scale, process development efforts are aimed not at creating a supply chain, but at enabling preparation of the API on schedule with a reasonable amount of effort. The synthesis route can be the same as used by medicinal chemists, but the solvents and reagents are often changed and the volume of solvents reduced.

In Phase II trials, the quantities of API needed are normally 10–100 kg. Manufacture of these quantities requires the capacity of a pilot plant and, for long synthetic routes, even a small-scale manufacturing plant. Something similar to a supply chain must be assembled, even if it is for a one-off operation. A significant process development effort might be needed to allow sufficient supplies to be made at all. The need for chromatographic purification of intermediates and the product has to be minimized and perhaps a more robust synthesis than the original medicinal chemistry route has to be found. The attrition rates at Phase II are a staggering 50–65% [1]. As few as one-third of the candidates that start in Phase II clinical trials make it to Phase III.

Phase II is usually the last stage of the drug development project to introduce a new synthetic route without delaying the launch of the drug, should it survive the stage. New routes will probably present new impurities in the API. Safety evaluations of API with the expected impurity profile are usually initiated during the early stages of clinical trials, and are therefore easy to arrange; however, they are often difficult to schedule in the late stages of clinical trials. Process development efforts at Phase II must focus on control of these impurities, with the attention first on the synthetic steps that form the API and then to steps that form the intermediate compounds. Furthermore, drug regulators now require 6–12 months worth of stability data, on drug products and substances made by the commercial process at large scale, to be filed with the New Drug Application (NDA) or the drug dossier [5]. In effect, a drug developer must begin establishing the commercial supply chain at the very start of Phase III studies, leaving very little time for route exploration during this phase.

At the final stage of clinical trials, Phase III, the attrition rate is much lower but still significant, ~20% [1]. The workload in process development is heavy, fully defining the process in all details, identifying the critical process parameters and their limits, finding and qualifying vendors for advanced intermediates, establishing the final specification sets, preparing process validation protocols and designing new process facilities.

For every project, there are two competitions for resources: other projects at roughly the same stage and other projects at different stages. The process development dilemma is, therefore, twofold.

Any resource allocation strategy must allow decisions to be made on which stage of development, and which projects at each stage, need the most attention.

Less than half the drug candidates survive Phase II and yet a significant, and sometimes a very heavy, process exploration and development effort must be expended on the candidates. The result must be a commercial-ready process, even if the candidate proves to be commercially unfeasible. Balancing the demands of Phase II and Phase III projects can be difficult. Phase II projects in trouble impose an urgent demand for attention, but Phase III projects are almost always important and are particularly visible to senior management.

Possible strategies to balance demands

Often a firm's strategy to manage resource allocation is not explicitly stated but, in effect, 'this is how we do it.' To illustrate some of the common approaches, I have described five strategies.

Strategy 1: 'Crisis management'

This is a strategy of triage, appropriate when a process development group is being overwhelmed and must choose between support or no support. If the unsupported projects are not significantly delayed by the momentary lack of attention, and the resources are focused on projects that are lagging, this is just common sense project management.

However, this strategy is easily misused. If the criterion of triage is no longer a choice between 'can get by' or 'can't get by' and becomes a choice of 'not-hot' or 'hot', the strategy can be very wasteful. If the development group could predict which projects will advance

and which will not, the strategy would work brilliantly. Unfortunately, nobody can really identify the winners and losers in the middle stages of clinical trials.

Permanent triage tends to devolve into the strategy of 'Pick a winner', in which all resources are focused on the hot projects. A destructive symptom of 'Pick a winner' is assignment thrashing. Scientists are assigned to one hot project only to find themselves reassigned to a new, hotter project three weeks later, with little progress to show.

Strategy 2: 'Manufacturability' or 'Developability'

Difficult-to-manufacture compounds would be nipped in the bud before any development resources were spent on them. Some firms even propose to limit the discovery search to classes of compounds that are deemed easy to develop. 'Developability' is a concept that includes the ease and cost of manufacture as well as other obstacles to development, such as poor solubility.

It is important that decisions about the 'manufacturability' of a drug candidate are not made too early. Almost every drug has appeared hard-to-make at one time in its development cycle.

As an example, a client of my firm presented a data table showing a comparison of the biological assay results of two candidate compounds from their discovery program. One was clearly superior, but the client asked us to prepare a sample of the inferior candidate for pre-clinical testing. When the client was asked why the inferior candidate was wanted, we were told that the superior candidate was obviously going to be too expensive to make. An analysis by our process chemists showed that this first impression of the manufacturability of the superior candidate was not necessarily true. Our process insight allowed the customer to reconsider their choice of candidates.

Unlike solubility and other aspects considered in assessing the developability of a compound, manufacturability is not an intrinsic property of a molecule, but instead a reflection of the current technical capability of manufacturing. I have seen projects stalled by what seemed insurmountable practical manufacturing barriers. Those barriers were then swept away by a concerted process development and manufacturing design effort. If the compound cures, a way will be found to make it.

Strategy 3: 'No process development work until Phase III'

One way to manage resources at Phase II is to use the process at hand to make enough clinical supplies to get to Phase III without any process development. No work would be wasted on dead-end candidates, enabling all available resources to be used for the projects near commercialization.

If the Phase II process proves impractical, this strategy could lead to a delayed filing, perhaps as long as a year, because the required data for the Chemistry, Manufacturing and Controls (CMC) section might not be available when the rest of the NDA is ready to file. It also withholds a process development effort to unblock the bottlenecks frequently encountered by the clinical supply operations at Phase I and Phase II. This strategy will slow down the whole pipeline if rigidly applied to all projects.

Even with its many drawbacks, this strategy can serve a firm well. Some drug candidates are simple, readily made compounds; some are highly potent or serve small patient populations and only small quantities are required. For these projects, the clinical supply requirements can be readily met with an undeveloped process and, often, that process can be practically implemented for commercial manufacture with only minor improvements. There might be no need to do any more development work than necessary to prove the process can, in fact, be successfully executed and controlled.

Our firm has been contracted to prepare commercial goods at a very small scale, just a few grams per year. The project was already at Phase III when we were contracted, and no significant process development had been done. After analysis, we found that a more efficient synthesis would not deliver much value for the effort and expense. The development work that was needed focused on finding the critical process parameters and their proper limits, and on establishing the sources of materials – the typical Phase III program.

Strategy 4: 'Develop everything'

This strategy dictates that process development is conducted on every candidate. Usually a project manager is appointed at the Phase I to Phase II transition or even earlier and given the resources needed to drive the project forward. No candidate is allowed to languish so that others can be advanced. If resources are available for this, many benefits follow; for example, rapid submission of the CMC section and technology transfer to manufacturing [2], and a ready supply of clinical materials for every project.

However, aspects of the dilemma could still be present at the project level. The project manager is left with the problem of balancing short- and long-term goals: whether to deploy resources to solve the immediate needs for clinical supplies or to perform the hard work of creating a supply chain.

One major firm tries to find at least three routes for each compound at Phase II. The routes are carefully examined and one is selected to advance the compound through Phase III and into full-scale manufacturing. It could be argued that this degree of effort is excessive, but this firm rarely finds itself without clinical supplies or the delay of an NDA submission to let the process development work catch up.

Strategy 5: 'Portfolio management'

A drug pipeline can be viewed as a venture capitalist's (VC's) portfolio and,

similar to a portfolio of investments; some drugs are profitable and most fail. And, again similar to a VC's portfolio, there is great value in speed and turnover. It is crucial that bad investments are killed fast and that good investments are moved ahead as quickly as possible.

Process development can contribute greatly to the rate at which a portfolio turns over. The simplest and most effective way to marshal resources under this strategy is to keep clinical supply production and commercial development milestones off the critical path of all the projects in the portfolio.

This strategy, in a sense, dispels the process development dilemma altogether. Under other strategies, the effort expended on commercial dead-ends is just a wasted resource. A drug pipeline VC values that effort on dead-ends because it increases the velocity of the portfolio turnover. Of course, an increased portfolio turnover rate is truly valuable only if the firm has a vigorous drug discovery effort that can replace a fallen project with a new one.

My firm works for a client that uses the 'Portfolio management' strategy. We were taken aback by our client's cheerful, almost celebratory, announcement that a project had been cancelled. Sensing our bewilderment from the pregnant silence over the telephone, our contact replied, 'Oh, you see, we got rid of another dog.' The goal is to move the projects to a decision point, and then push on to the next point if the answer is not yet 'no'. Successful management of the portfolio is really a race to the answer 'no', hoping the answer is 'yes', but accepting a quick 'no' as the next best thing.

Discussion

Choosing the correct process development strategy is an important decision. To get it right, management must consider the state of the pipeline, the types of challenges posed by compounds in the pipeline, and the development resources that the firm can afford.

'Crisis management' holds a program together until more resources can be brought to bear and, as a temporary measure, it is rational. Unfortunately, long-term 'Crisis management' and the 'Pick a winner' variant are all too common and very wasteful. These are the strategies of a firm with no real strategy.

'Manufacturability' selection policies are not common among major pharmaceutical companies. A good molecule is hard enough to find without adding another hurdle that can be overcome by process development. A small firm sometimes sells off the rights to a compound that could consume more process development resources than it can afford, keeping only those that the firm has the expertise to develop. For those compounds that remain, the firm must still find an appropriate strategy.

The 'No process development work until Phase III' strategy might be appropriate for a portfolio of drugs with low annual volumes, where efficient manufacture is not as crucial and where it is not difficult to satisfy the clinical requirements. This strategy dictates an emphasis on late-stage compounds with no attempt to favor one late-stage project over another.

The 'Develop everything' strategy becomes 'Develop nothing' at a firm lacking the resources to execute the strategy correctly. Similarly, 'Portfolio management' will resemble 'Crisis management' if the process development staff is too thin to chase all the clinical supply deadlines off the project paths. It would be far better to recognize that resources are limited and get more help, sell off or stop some projects, or simply accept the risk that some launches might be delayed. Because they lack a pipeline to justify process development departments to execute either 'Develop everything' or 'Portfolio management' strategies, many small firms defer process development and leave the work to the company that buys the candidate; they outsource process development only for those compounds they keep.

The 'Portfolio management' strategy is subtly different to 'Develop everything'. 'Develop everything' focuses on the projects. Resources are supplied to advance each of them, with most decisions being made at the project level. The focus of 'Portfolio management' is on the portfolio. Resources are applied to advance all of the projects as needed, to keep clinical supply and process development issues from affecting the time of launch of any product, with many decisions being made at the VC level. The 'Portfolio management' strategy might work best in a firm that is centralized, whereas 'Develop everything' might be more suited to a firm with decentralized management.

Conclusion

Process development is a valuable resource that not only saves capital and manufacturing expense, but also moves products out of discovery stages and onto the market more quickly. It should not be squandered by misapplication of process development strategies, spreading resources so thinly that real process development does not get done or is wasted through a lack of focus on the true goals. Failure to get the strategy right leads to shortages of clinical supplies, delays in the launch date, and an unstable supply chain.

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