

SOLUTION DEVELOPMENT

A Model For Structuring Biotechs And Developing Better Drugs

Industry must think differently about funding high-risk/reward development of drug candidates against novel targets. Multiplexed Phase II proof-of-concept trials can light a path toward lower-risk pivotal studies and provide a model for building biotechs to deliver what patients, providers, payors, and investors all want: solutions.

BY PETER KOLCHINSKY

- Current models of biotech drug development are inefficient and often fail to ask difficult questions at the proof-of-concept (POC) stage, resulting in inadequate de-risking and weak late-stage candidates.
- If a company were laser-focused on a single well-chosen indication and several of its best Phase I candidates were advanced together into the same Phase II program, the odds of overall POC success would be higher than for a typical single-drug Phase II study, and mediocre drugs that merely beat placebo but not other drugs would be less likely to get to market, sparing patients' disappointment and investors' capital.
- This Solution Development model offers a way of reconciling a company's desire for diversification across multiple drug candidates with investors' desire for a company to focus on its best program.
- Biotechs may be at the center of the Solution Development model, but there are intriguing roles for Big Pharma and non-profits in assembling drug candidates and incentivizing their developers in future multiplexed proof-of-concept trials.



The drug companies that have the hardest time raising capital to fund proof-of-concept research are the ones developing drugs against new targets. The irony is that in an industry that ostensibly strives to be innovative, investors hate risk and would prefer to invest in a reformulated (e.g., **Alkermes PLC**), repositioned (e.g., **Cypress Bioscience Inc.**), geographically relocated (e.g., **Amarin Corp. PLC**), relaunched (e.g., **ViroPharma Inc.**) or reprinted drug (e.g., **Questcor Pharmaceuticals Inc.**) or enzyme replacement therapy NCE (e.g., **Synageva BioPharma Corp.**). These companies and others are successes in their own right but too exceptional to serve as role models for how our industry can continue to tackle large unmet health care needs in the coming decades. Such companies can raise money for a single validated agent; in fact, investors typically prefer that they focus on advancing one drug through later-stage trials and not divert any cash to an early-stage pipeline. (See “How To Create A Lasting Peace Between Biotech Management, Shareholders And Employees” — IN VIVO, July 2011.)

Yet it is likely that only innovative but riskier approaches can lift industry out of its current doldrums, providing the necessary advantages over current standards that will convince payors to agree to premium prices and generate the returns necessary for continued biotech investment.

One such path, described below, points to a new model of drug development and company building whereby biotech companies define themselves by the problem they aim to solve and not by the most advanced drug candidate in their pipeline. This Solution Development concept relies not simply on pulling together a stable of drug candidates in a particular therapeutic area, nor on building companies around other organizing principles like chemistry, technology platform, or type of drug target. Instead, it relies on assembling a set of candidates at the same or similar stage of development that address a specific, precisely defined indication and pitting those candidates against one another and a control in an unusual but powerful proof-of-concept study: the multiplexed Phase II trial.

Companies will typically take many molecules against the same target into animal models, move several through IND-enabling studies, and maybe even put a couple through Phase I. But once they

embark on Phase II studies, the majority of biotech companies and even some smaller pharma will commit themselves to one particular drug candidate, even as the target problem morphs in response to an evolving standard of care, new market entrants, shifting regulatory hurdles, and reimbursement barriers. They don't stop until a trial actually misses its endpoint (and even then many keep going thanks to non-prespecified analyses), the FDA rejects their candidate, or they wreck themselves trying to commercialize the product on their own, all based on little more than data suggesting the product is better than placebo.

If the bar for succeeding in Phase II is

ter than placebo but also comparatively better than other agents in terms of efficacy, safety, and convenience. In other words, better equipped to hack it in the real world.

The Solution Development model is also a way of reconciling a company's desire for diversification across multiple drug candidates with investors' desire for a company to focus on its best program. Before Phase II, when less is known about any one drug, the Solution Development



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rising, then the odds of success of any one drug are likely to be lower than ever, especially when a company rises to the challenge by developing novel drug candidates against novel targets. It may be necessary to identify multiple active agents and combine them to get good enough efficacy to compete commercially. Novartis, for example, is taking this concept to the extreme by testing thousands of candidates in various combinations on hundreds of cancer cell lines to identify combination therapies suited not just to a particular cancer but to a genetically defined tumor or even multiple, genetic sub-populations of a single tumor. Most biotech companies, in comparison, are still flogging one drug.

One of the major causes for the high cost of drug development is that companies subject their drugs to very little negative selection before bringing them to market, merely demonstrating that they beat placebo in most cases, and therefore end up competing feverishly in the commercial setting where most discover that an FDA-approved drug isn't necessarily “real-world approved.” Making drug candidates compete with one another through Phase II development will greatly improve the odds that the drug that comes out ahead is not just bet-

ment company is diversified across multiple candidates and the chances of at least one drug beating placebo is higher than if it had only one drug entering a Phase II trial. But after a proper multiplexed Phase II, when much more is known about each drug, logically, management and investors (and maybe partners) will want to advance only the best candidate into Phase III trials.

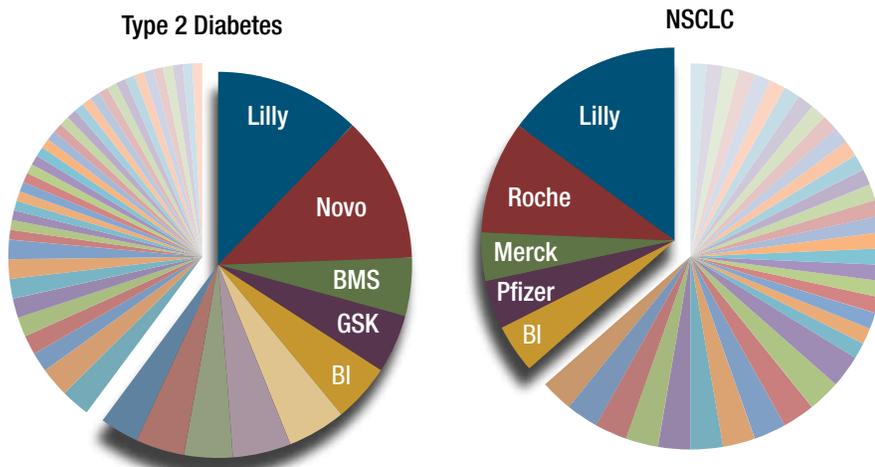
Imagine three companies A, B, and C each with one drug in its pipeline for each of three disparate indications: cancer, rheumatoid arthritis, and diabetes. Each company considers itself to be diversified across three different drugs for three different indications. However, each one is duplicating the efforts of the others and, even if all the drugs beat placebo, they are not likely to all succeed commercially.

Now imagine if Company A developed all three cancer drugs in parallel, Company B developed all three rheumatoid arthritis drugs, and Company C took charge of diabetes. The efforts of each company would be focused on a single task and each three-plex Phase II proof-of-concept trial could demonstrate not only which drugs perform better than placebo, but also which drug performs best of all. The end result would be that each company would have a better shot at creating a commercial winner without duplication of effort and waste of resources.

Exhibit 1

In Diabetes Or In Non-Small Cell Lung Cancer, Many Companies Compete With A Single Candidate

At least 48 different biopharmaceutical companies are pursuing clinical-stage treatments for type 2 diabetes. In non-small cell lung cancer, 41 different companies have drugs that are in Phase II or beyond. Only a handful of competitors – typically the largest companies – are pursuing multiple agents against the same disease. Here only the companies with the largest baskets of assets are identified.



SOURCE: TechAtlas

CURRENT MODELS LACKING

Drugs against new targets have certainly been tested in the last decade, but in many cases the companies that developed them, for example **Human Genome Sciences Inc.**, were able to tap massive amounts of money that they had raised during the platform-partnering era and/or the genomics bubble not explicitly for the purpose of themselves taking drugs through POC trials. Once such a company has good POC data for one drug candidate and needs more capital, then investors switch to viewing it as a late-stage drug development story and may be happy to step in to fund the rest of development, assuming other elements are in order: the market is attractive, regulatory issues are tractable, etc. Not all genomics platform companies were fortunate enough to have a Phase II success and switch over to being a drug company; the ones that didn't adapt have largely disappeared.

Some companies have early-stage candidates that modulate novel targets but they do not have enough cash to fund POC trials. Barring some serendipitous Phase I finding that significantly de-risks the endeavor, the company may not be able to raise capital from investors, who typically want proof of efficacy but are reticent to pay to

get it. Pharma has a relatively low cost of capital and periodically will fund early-stage development by smaller partners if it has an interest in a particular target (hence the rise in GSK-style option-alliance dealmaking over the past decade), but otherwise these companies typically rely on government grants or non-profit funding to keep their programs alive. But can they do better?

They'll have to in order to survive. Just about every bar there is in drug development is higher now than it ever has been.

There are more great generic drugs than ever before and patients are better managed. Many once-scary diseases have become so well managed, for example HIV and breast cancer, that efficacy is merely a ticket to compete; only great safety, tolerability, and convenience will win the race. Europeans demand active controls and reference pricing. In the US, comparative effectiveness is gaining traction, biosimilars are now a reality, and even physicians may lobby against what they see as price gouging; **KV Pharmaceutical Co.**'s pricing of *Makena* (hydroxyprogesterone caproate) is a cautionary tale. (See "FDA Steps Into Makena Pricing Dispute In The Name Of "Access"" — "The Pink Sheet," April 4, 2011.) The FDA and payors are more pragmatic than ever, demanding that drugs demonstrate benefits

on endpoints that actually matter, such as survival in cancer, not response rates.

Meanwhile, there are great inefficiencies throughout industry, particularly in hot therapeutic spaces. (See Exhibit 1.) Instead of dozens of companies each developing a single agent for a particular indication (especially when some of these companies interpret every hint of efficacy as justification for plowing forward), competing for patients, investigators, dollars, and hope, better that there be fewer companies each developing multiple agents in parallel so that they could afford to set the mediocre candidates aside and advance only the best one.

This model makes sense because what patients, physicians, and payors want is a solution. No one actually cares about what is in the drug itself. A therapy is judged not by the science but by its profile: "Does it cure my disease? Will I experience side effects? How often do I have to take it?"

LEAKY INVESTMENT LOGIC

Investing in biotech historically has been akin to betting that a plumber with one tool could fix a leak. Worse, some companies held themselves out to be all-in-one plumbers, piano tuners and electricians but came prepared only with three wrenches of different sizes. Imagine sending dozens of these under-equipped jacks-of-all-trades to plug a leak. What's needed is for a plumber to show up with a well-stocked tool box.

In the prostate cancer space there are a variety of competitors on or close to market, each with only one agent. (See Exhibit 2.) Dozens of other companies are pursuing drugs in earlier development. In most cases, a company's prostate cancer agent is just one of several programs it has in development for various disparate indications; in some cases the prostate cancer agent is its primary program and in other cases it is further down the pipeline. These companies are not running superiority studies against each other's agents. They are trying to fit their drugs into a sequence, just after patients fail one standard-of-care agent and maybe in combination with another. If they all had their way, patients would go on 20 different drugs between being diagnosed with prostate cancer and death. That's untenable unless most of those drugs are generic – and even then it's far from desirable. Increasing the negative selection pressure on industry's drug candidates at an earlier stage would vastly reduce the overall cost of drug development.

Exhibit 2

Prostate Cancer Drugs: Recently Approved Or In Late-Stage Development

Prostate cancer therapies in development don't typically compete against one another ... until they reach the market. Superiority studies in clinical trials would reduce this inefficiency and boost the winner's chances of commercial success. Below is a list of recently approved agents and candidates in Phase III trials.

DRUG/DRUG CANDIDATE	DEVELOPER/MARKETER	DEVELOPMENT STAGE
Jevtana (cabazitaxel)	Sanofi	Marketed
Xgeva (denosumab)	Amgen	Marketed
Provenge (sipuleucel-T)	Dendreon	Marketed
Zytiga (abiraterone)	Johnson & Johnson	Marketed
Enzalutamide (MDV3100)	Medivation/Astellas	Registration
Alpharadin (radium-223 chloride)	Algeta/Bayer	Phase III
Yervoy (ipilimumab)	Bristol-Myers Squibb Co.	Phase III
Orteronel (TAK-700)	Takeda/Millennium	Phase III
Custirsen (OGX-011)	Oncogenex/Teva	Phase III
Tasquinimod	Active Biotech	Phase III
Prostvac	Bavarian Nordic	Phase III
Cabozantinib	Exelixis	Phase III

SOURCE: *Strategic Transactions*; Company reports; clinicaltrials.gov

WHY INVESTORS PREFER SINGLE-INDICATION COMPANIES

Companies often have a hard time inspiring investors to back more than one program because it's difficult for two ambitions to co-exist in one pursuit. People tend to pick their favorites. There are many non-profits out there pursuing worthy causes, but each person is likely to favor only a few. If a non-profit were to tackle two causes and then go hunting for donors, it would find that a large percentage of those who like one cause don't like the other, making it harder to raise money than it would be for a non-profit focused on a single, compelling problem. The same principle applies to a company. Define yourself by the problem you aim to solve and identifying the people who will support you will be straightforward. If every problem had its own company, investors would find it easy to construct a portfolio of companies that perfectly represent their unique combination of priorities.

When a company does try to pursue drug development for more than one indication, investors generally focus on the most advanced and/or most valuable candidate and distill the company's valuation and identity down to that one program. If two or more candidates are both in Phase II trials, they will often look at the timing

of proof-of-concept data, focus on which-ever candidate will read out data first, and write off the other programs as merely "a pipeline." They assume that the company will sink or swim based on the outcome of the first program to yield major data. If that program fails, the company's valuation will plummet and investors will revisit the pipeline to see if there is anything of value; investors might then invest in the advancement of the next candidate at a lower valuation. If the lead program succeeds, the fate of the rest of the pipeline won't matter. Either way, the pipeline is not relevant to the decision to invest ahead of the data readout from the first program.

Indeed, given the choice between a highly valued single drug and a pipeline/platform, the lead drug nearly always wins; in fact, if the lead drug hits a rough patch, often everything else is jettisoned, as illustrated by companies like **Exelixis Inc.** and **Arena Pharmaceuticals Inc.** (See "*Exelixis Slashes Staff Again, Focuses All Internal Development on XL184*" — "The Pink Sheet" DAILY, December 2, 2010.) And if the lead drug is successfully commercialized, then activist investors or acquirers often prevent management from trading very real cash flows "in the hand" for pipelines promises "in the bush," as many

companies have discovered. Very few are entrusted with reinvesting cash flows from one drug into development of new drugs. The few exceptions usually are allowed to do so until they make a few mistakes, and then shareholders agitate for the cash to be returned through share buybacks, dividends, or sale of the company. Trusting biotech management teams with cash flow has not been a profitable strategy for investors, so they find it reassuring, once a company has a good candidate in hand, if the company is "built for sale" rather than "built to last," and that means no pipeline (with the exception of backup analogs to the primary asset).

Market forces conspire to make most companies channel limited resources to one purpose, making diversification across multiple indications and drugs challenging.

DIVERSIFICATION AND FOCUS, EACH AT THE RIGHT TIME

Just about the only companies in which a diversified pipeline is tolerated are those with early-stage candidates where investors do not know enough about any one candidate to channel the company in a particular direction. Of course, if the company is seen as unfocused, investors might not fund the company to go in any direction.



Defining the unmet need is the single most important thing that a company must do; an entrepreneur cannot escape his or her responsibility to define a worthy and appropriate problem, one that is both inspiring and tractable.

If all of a company's drug candidates were laser-focused on a single well-chosen indication and were advanced together into the same Phase II program, then the odds of overall success would be higher and management could afford to focus only on its best candidate. According to drug development probabilities published by **Tufts University's Center for the Study of Drug Development**, the average drug candidate has only a 30% chance of success in Phase II, which means a 70% chance of failure. Running a single multiplexed Phase II trial with three well-chosen candidates would therefore result in a 66% chance of at least one drug being successful ($1 - 0.7^3$), a dramatic improvement in clinical trial odds over a typical one-drug Phase II and therefore far more likely to be compelling to investors. Such probabilities are simplistic and certainly vary with the problem in question, but there are clear advantages to linking multiple, lower probabilities into a single, larger probability of a successful data readout.

The Solution Development model offers diversification across several innovative candidates in the pre-POC stage when so little is known about any one of them that to bet the company on just one would be too risky for most investors. Once a multiplexed Phase II trial is completed, inves-

tors and management would be aligned in wanting to focus further spending and development effort on the best candidate (any other candidate that beat placebo would be kept warm as a possible backup in case the lead stumbled later).

Of course, to start with, each of a Solution Development company's candidates must be selected as carefully as if it was the one and only molecule the company had; diversifying across garbage will still result in failure akin to the housing subprime mortgage crisis. Therefore, a Solution Development company must not lower the bar for a drug candidate to qualify for a multiplexed Phase II. Likewise, investors and prospective partners must hold each drug to a reasonable standard of pre-Phase II validation; the drug must have demonstrated activity in a validated animal model, have showed good safety in animal studies, and have a high maximum tolerated dose with an acceptable dose-limiting toxicity profile. To reduce the chances of the drug candidates all failing for the same off-target or on-target toxicities, they would ideally have different chemical backbones and modulate different targets or even pathways.

The model also avoids a common problem associated with companies pursuing a "shots on goal" strategy: engineering data convergence on a single day spares the company and investors the roller-coaster ride of finding out which compounds failed and which succeeded at different points in time. (See sidebar, "Optimizing Behavioral Finance Theory.")

DEFINE THE PROBLEM, DEFINE THE RIGHT PATH

Ideally, the only risk factors common to all the early-stage candidates would be the management team that selected them and the choice of indication, which are the essential elements of a Solution Development company's identity. One might fear that the company chose the wrong indication, but if a management team cannot get that right, then it should expect to fail. Defining the unmet need is the single most important thing that a company must do; an entrepreneur cannot escape his or her responsibility to define a worthy and appropriate problem, one that is both inspiring and tractable.

Many companies form around all sorts of platform technologies, formulation science, drug targets, or therapeutic areas. They have perfectly specialized chemists

or formulations experts or biologists. But these organizing principles often tear clinical teams in many different directions.

A company that truly specializes in spinal cord injury (SCI), for example, and that has three disparate ideas for how to spare spine trauma victims from becoming paralyzed, is more likely to succeed at its mission than a "neurology" company that is developing drugs for stroke, SCI, and seizures. Focusing on "neurology" is like a researcher focusing on "biology"; being successful requires a far greater degree of specialization in the disciplines involved in achieving an important goal. An SCI Solution Development company would likely have enough at stake in defining its objective carefully that its SCI-focused clinical team would have spent all its time optimizing the entry criteria for the ideal POC study and endpoints that would appeal to investigators, FDA, payors, ethicists, and, most importantly, patients. Unfortunately, like the hypothetical diversified "neurology" company, most ordinary biotech companies spread themselves thin, define themselves by anything other than a target indication, and end up effectively dabbling in each area into which they venture.

INCHING TOWARD SOLUTION DEVELOPMENT

It's not easy to find examples of multiplexed Phase II trials, but the Solution Development concept is not new to pharma. In a COPD collaboration with **Theravance Inc.**, **GlaxoSmithKline PLC** conducted a Phase II trial of two separate candidates (i.e., a two-plex Phase II), comparing one with the other and also with a control. The factorial trial, a close cousin of the multiplex trial, tests a combination drug against its separate components and a control, a strategy pursued by a variety of biotechs including **Pharmasset**, **Vivus Inc.** and **Orexigen Therapeutics Inc.** **Eli Lilly & Co.** and **Roche** have multiple drug candidates in each of diabetes and lung cancer and are therefore able not only to identify the best single agent of the group but also to experiment with combinations pre-commercialization. Pharmas are even partnering to combine their pipelines – or at least to test them in combination without sharing economics (e.g., **Merck & Co. Inc./Roche** in HCV, **Merck/AstraZeneca PLC** in oncology, **GSK/Pfizer** in HIV). (See Exhibit 3.) Unfortunately, anything resembling the Solution Development model is rarely deployed in biotech, but there are a few exceptions.

Exhibit 3

Large-Scale Solution Development: Peer Dealmaking Among Big Pharma

Large pharmaceutical company peer deals to test individual assets in combination or to pair entire stretches of pipeline allow companies to share risk and increase their chances of commercial success. A few variations on peer dealmaking, described below, are likely to be emulated as larger companies grasp for models to improve R&D productivity.

DEAL	DATE	DESCRIPTION
Merck/AstraZeneca combine early-stage oncology assets	June 2009	In what was considered a first of its kind collaboration, Merck and AZ agreed to research combining their respective candidates AZD6244 and MK2206 into one therapy for solid tumors. The companies will work together through Phase I testing and then consider future opportunities. Development costs are equally shared.
Pfizer and GSK form Viiv Healthcare Joint Venture	November 2009	The two large pharmaceutical companies merged their HIV marketed products and commercial infrastructures to create Viiv. The ownership stakes were determined by respective cash flows (and may be tweaked based on achievement of regulatory or sales milestones) and while individual pipeline assets remain the property of the originators, Viiv covers certain expenses and retains options on those projects.
Roche/Merck study HCV combination therapies	May 2011	As part of a deal that includes a non-exclusive co-promotion agreement around Merck's <i>Victrelis</i> (boceprevir) HCV protease inhibitor, Merck and Roche scientists will work on new and improved combination treatments using HCV agents from each partner's portfolio.
Lilly/Boehringer team up in diabetes	January 2011	The drugmakers will develop and commercialize a portfolio of diabetes drugs in mid- to late-stage clinical trials. The program includes two oral diabetes drugs from BI, linagliptin, a DPP-4 inhibitor, and BI10773, an SGLT-2 inhibitor, and two basal insulin analogues from Lilly: the novel basal insulin LY2605541 and an insulin glargine product LY2963016.

SOURCE: *Strategic Transactions*

Consider how **Achillion Pharmaceuticals Inc.** and **Idenix Pharmaceuticals Inc.** each have several anti-HCV drugs in early development. Recently, Achillion set aside one NS5A inhibitor that another company might have considered adequate, but management preferred a more potent one in its arsenal that would likely combine well with one of its two protease inhibitors. Pharmasset, recently acquired by **Gilead Sciences Inc.**, had several HCV polymerase inhibitors and tested two nucleotides nearly in parallel; one did well and the other failed due to toxicity. Had Pharmasset's two drugs been developed by two separate companies, there would have been one winner and one very pained loser; instead, there was just Pharmasset.

Vertex Pharmaceuticals Inc. was essentially the first HCV company to hit it big, enjoying a massive \$3 to \$5 billion valuation well before 2010, when other HCV companies started to come into their own. What kind of HCV company would Vertex be now if it had used its massive valuation to roll up diminutive peers like Pharmasset, Anadys, Inhibitex, Idenix and Achillion, aggregating whatever available drug candidates it might need to dominate

HCV for the long run instead of simply being early to market with the one drug it had, telaprevir, which likely won't be commercially relevant after 2014? Ultimately, Vertex did pick up a few additional assets and may yet retain an important role in the HCV space, but starting earlier with a Solution Development framework would have likely left Vertex far better positioned than it is today.

From among all indications, HCV may be an exception. It lends itself to faster and cheaper POC studies; early indicators of efficacy in Phase I are highly predictive of Phase II success. Furthermore, because of the size of the HCV market and rapid development timelines, pre-Phase II HCV companies today enjoy larger valuations relative to their capital requirements, resulting in a lower cost of capital, than companies in most other fields.

And although perhaps not intending to demonstrate a novel business model for others to emulate, **Verastem Inc.** may have been the first Solution Development start-up when it licensed in disparate early-stage compounds, all with activity in the same cancer stem cell model, and targeted them all at triple negative breast cancer. While

none of the individual compounds offered much in the way of data, management inspired investors to fund development of three compounds up front all the way through a Phase II trial with PFS and survival endpoints. Atypically, that promise helped to raise \$59 million in a successful January 2012 IPO. What happened next was possibly a more standard biotech play. In July 2012, Verastem licensed in a Phase II/III-ready FAK inhibitor from Pfizer and focused its efforts on starting a registration study in mesothelioma. Although the transaction made Verastem a later-stage company, the FAK inhibitor is likely to become investors' sole focus, or will at the very least pull attention and funding away from the company's multiple triple-negative breast cancer drug candidates.

An ongoing example of parallel development of multiple compounds for the same indications is Vertex's CFTR corrector program for cystic fibrosis. Both VX-809 and VX-661 are in controlled POC studies, albeit separate ones, in combination with Vertex's other CFTR drug, the potentiator *Kalydeco* (ivacaftor). Having so many compounds in development allows Vertex to experiment with combinations that would not be avail-

able to companies that put all their hopes on a single candidate. (See “Vertex’s CF Therapy Combination Trial Yields Promising Lung-Function Data” — “The Pink Sheet” DAILY, May 7, 2012.)

THE POWER OF MULTIPLEXING

The Solution Development model and its primary clinical instrument, the multiplexed Phase II trial, offer a means for bringing better drugs to market more cost-effectively than we have in the past with greater buy-in from investors, physicians, patients, regulators, and payors.

Imagine a three-plex Phase II (three drug candidates) with two arms per agent to allow for different doses or dosing regimens (BID vs. QD) such that it had six active arms and one control arm. Such a trial would be better than a regular single-drug Phase II on many fronts with only a handful of manageable disadvantages, including cost, complexity and blinding.

It takes a lot of effort, time, and therefore money to design the right Phase II study. A three-plex Phase II would no doubt be more expensive and complicated than one that tested a single agent against placebo, but it wouldn't be three times as expensive since not all clinical trial costs scale proportionately to a trial's size. The greater investment of time/effort/money would actually result in less of each per

compound, especially when taking into account the theoretically lower cost of capital for a company pursuing this design, given investors' embrace of this greater chance of success.

This theoretical trial would also have advantages in patient recruitment. Patients do not want to enroll into a placebo-controlled trial. It takes a lot of effort for an investigator to explain to desperate patients that, if they want even a chance of getting an experimental drug, they have to risk being randomized to a control arm. Letting placebo patients cross over to the experimental drug is sometimes one solution to convincing them to accept randomization to placebo, but this isn't always possible, as in the case of survival studies, without confounding the endpoint analysis.

In the three-plexed Phase II with two doses of each drug and one control arm, patients might be inspired to participate by their greater likelihood of getting an experimental drug (six out of seven arms). Statisticians would point out that by using a single control arm for assessing the effectiveness of six experimental arms, there is a greater chance that an unusual placebo response rate in the control arm could simultaneously make all three drugs look inappropriately too good or too bad. But even if the control arm were doubled in size so that it enrolled 25% of the patients,

that still gives patients a 75% chance of getting an experimental agent, which are better odds than if the Phase II were testing two doses of a single agent versus placebo and therefore gave patients only a 67% of being in an experimental arm.

And not only do multiplexed trials offer greater probability of success, they also can increase the quality of a success with comparative effectiveness data; the winning drug will have been battle tested against not only placebo but also against other candidates. Multiplexed trials would result in drugs that are better vetted for competition in the commercial arena, where a drug has to be good enough for patients and payors, and not just good enough for statisticians.

If a three-plex Phase II showed that more than one agent were active, resources could be concentrated on advancing the best of them into Phase III development, improving the odds of commercial success and the return on investment (ROI). If the best drug then fails in Phase III trials, possibly due to toxicity, then the second best drug from three-plex Phase II would ascend to being best and might be a candidate for further development. Using adaptive trial designs, resources could even be shifted during the three-plex trial itself, moving patients away from drugs and doses that showed less promise. Were the multiplexed Phase II Solution Development model to be adopted

OPTIMIZING BEHAVIORAL FINANCE THEORY

When a company attempts to interest investors in more than one development program, it subjects itself to a somewhat complex interplay between investors' desire to have multiple shots on goal and their tendency to distill a company down to its lead program.

For example, **Omeros Corp.**, **PolyMedix Inc.**, and **Tranzyme Inc.** have been able to fund development of two agents almost in parallel. But it's impossible to time the results of two independent parallel studies perfectly, and a public company can't just sit on data while waiting for another trial to read out. As investors get closer to the data window for the two trials, they start betting on whether the first program will succeed or fail instead of looking at the overall odds of success of the two programs. Even if the trial results are only a few weeks apart, each day is an eternity as one gets down to the home stretch.

Many public funds are judged by their monthly performance and therefore hate to show even a paper loss. An aversion to the possibility of reporting a paper loss in the event of the first trial failing might prompt some investors to avoid the stock or sell it in advance of any data if they felt more comfortable with the second program's chances of success than with those of the first. If the two programs were somehow perfectly synchronized and data were announced on the same day (only possible with

a multiplexed trial), these same shareholders could hold the stock through the announcement knowing that they would be OK as long as at least one of the programs had good data.

The first of Omeros' program to read out data was successful. But PolyMedix and Tranzyme were less fortunate and lost half their market values when their first programs failed. If either needed to raise much cash to get to data from the second program, that would have diluted shareholders significantly and potentially permanently impaired the long-term value of the stock price. But they have enough cash to get to the results of the second program and therefore may yet recover their investors' paper losses.

In the case of a private company, it is not technically necessary to run a multiplexed Phase II for the purpose of engineering perfect data convergence. Since a private company's stock is only repriced when it raises capital, a company only needs to ensure that multiple programs read out data before a financing to be able to merge their chances of success into a single probability. But if it were to run a multiplexed Phase II program, then the private company could still enjoy all the other benefits of multiplexing addressed above as well as avoid the risk of one drug program getting significantly delayed relative to the others (from a behavioral finance standpoint, better they all get delayed together).

widely, the industry could be spared the waste of having companies launch secondary drugs simply because that's all they had.

Furthermore, competing companies, each with a good drug, tend not to test their drugs against one another, whereas a single company with two drugs worthy of bringing to market can run the proper studies to determine which drug should be used first. In other words, the Solution Development model affords companies intellectual honesty, an unfortunately precious and rare commodity. If the drugs can't be combined under one roof, then it would be desirable for companies to formally collaborate and jointly develop solution-focused pipelines, as was mentioned above.

LESS EXPENSIVE IN THE LONG RUN

Spending big for essentially one low-probability shot on goal is getting only riskier as clinical trials become more expensive and improvements in standard of care raise the bar for new agents. Therefore, companies that attempt to raise money to fund a Phase II for a single agent, whether from prospective partners or investors, are typically offered such financing, if it is offered at all, on unfavorable terms.

Investors and prospective partners often find that there is not enough known or even knowable about a Phase I drug to effectively assess its chance of having efficacy. Especially if the indication has been challenging to crack in the past, they might prefer to wait until the asset has been de-risked with data from a proper Phase II trial than to take a 70% chance of failure in Phase II. Sometimes, the decision to wait has less to do with the potential for financial loss than with the risk that the individual who champions the investment or partnership might look foolish if the Phase II fails.

But if asked to fund a three-plex Phase II trial, investors or a partner might find that fear of the unknown that can't be addressed with data can at least be mitigated through diversification. As long as each agent has a sound basis for being considered eligible for inclusion in the three-plex Phase II, then bundling all three to reduce the risk of total failure reduces the cost of capital for funding any one of individually (as well as reduces the actual cost per agent).

FINDING GOOD CANDIDATES

Creating a Solution Development company won't be easy. Just aggregating the assets, optimizing the trial design with

FDA and putting the sites and CRO in place to start the study would be a huge, value-creating endeavor. A pharma company might even purchase an option to acquire such a company even before the data from the multiplexed Phase II trial became known (or maybe before the Phase II itself was started).

But most companies are lucky to have one decent candidate to advance into a Phase II trial for a particular indication. How can a company get three? Clearly, business development will play a major role in assembling a good portfolio of drug candidates. However, it should be easier to talk another company with a preclinical or Phase I secondary asset into licensing it to a Solution Development company if both companies agree that this model is the best way to bring a drug to market. (*See sidebar, "Building a Solution Development Company Through BD."*)

SOLUTION DEVELOPMENT VERSUS THE SAME OLD INCREMENTALISM

Like the Apollo program to send a man to the moon, sometimes grand ambition alone is enough to inspire people to rally behind an expensive cause. Patients and investors are growing tired of "incrementalism" in the drug development industry: aiming just high enough to get FDA approval, only later to discover that the world doesn't really value yet another opioid, yet another reformulated migraine drug, or yet another cancer drug that delays death by a couple of weeks or months.

Better to hold all the promising candidates from across a half-dozen different companies to the same high standard than to let each company under-fund and under-validate its drugs in weak, poorly controlled Phase II trials. While it's possible that all the drugs put into a multiplexed Phase II trial will fail, at least that teaches us to look elsewhere for solutions. And if more than one beat placebo, then we will have some sense of which is better. Maybe one drug stands so much taller than the rest that we lose interest in the lesser candidates.

When it comes to some highly challenging indications such as Alzheimer's, even Big Pharma is guilty of doing weak Phase II trials before advancing candidates into Phase III. What if several companies had collaborated on conducting a large multiplexed and rigorous Phase II with several anti-beta-amyloid agents and had

set a properly high bar for efficacy (and the usual high bar for safety) over 18 to 24 months, a more meaningful time frame over which to assess progression than the typical 6- to 12-month Phase II trial? Might considerable waste on unwinnable Phase III trials have been avoided? Might the current beta-amyloid theory have been abandoned long ago in favor of one more nuanced and likely to be relevant?

A ROLE FOR NON-PROFITS

Non-profits and the NIH provide funding for basic research and early R&D, but many projects hit a wall as they become Phase II-ready because few non-profits can or will pay for the higher cost of a randomized, controlled trial. And yet, such data are critical to demonstrating which drug candidates hold true promise and which are false leads. A non-profit committed to addressing the needs of a particular patient group would likely spur far more early-stage R&D by directing its funding toward one large, multiplexed Phase II and setting clear specifications for the kind of data that would merit a drug candidate free or subsidized admission to the trial. The non-profit could tap the wisdom of the best researchers in the field to define particular preclinical animal model results and human pharmacokinetic data that companies could strive to generate by the application deadline.

This approach is neither necessary nor appropriate for fields like HCV that enjoy considerable investor and pharma support, have short POC trials, and are relatively tractable. Rather, a non-profit-sponsored multiplexed Phase II is meant to pull innovative candidates out of the early-stage R&D community that might not otherwise progress for lack of funding (e.g., spinal cord injury, neurodegenerative diseases, neuropathic pain, depression). Such fields are particularly ripe for multiplexed Phase II trials because that lack of funding tends to strand many candidates prior to proof-of-concept testing. Aggregating them into high-quality coordinated efforts would also be a good antidote to the kind of sloppy POC trials small companies run when they can't afford proper Phase II trials.

What the non-profit demands from and offers to applicants is an interesting question. One approach would be to promise that every company that wins a slot in the multiplexed Phase II trial by submitting a thorough and compelling preclinical and Phase I data package will be entitled to a small royalty on the sales of whichever

BUILDING A SOLUTION DEVELOPMENT COMPANY THROUGH BD

The hypothetical Spinal Cord Injury Inc. (“SCII”) is a company dedicated to running three compounds through a three-plex Phase II trial. At the outset, the company comprises a team of SCI experts and has a clear sense of what kind of product it wants – for example, one that could be administered as long as three days after an injury and still allow a person to recover enough function to be able to take care of him/herself. The team could then identify maybe six SCI preclinical and Phase I programs that are stuck in the pipelines of other companies that can’t justify the cost of advancing any one of these agents through a proper Phase II trial (maybe they have done small Phase II trials demonstrating an improvement in nerve conductance). SCII could offer each of these companies an equity stake, royalties, and/or milestone payments that would be larger for the Phase II-ready assets and lower for the preclinical assets because those would require SCII to spend money bringing them to the point of being Phase II-ready. Each contributing company could get a stake in the winning drug (if there ends up being one) with the actual originator of the winning drug getting a larger share.

The idea that SCII would now run a parallel development program for six of the best SCI drug candidates in the industry with the goal of putting the best three through a proper Phase II trial would likely grab the attention of many investors, partners, and non-profits. In fact, if another company were advancing its own drug candidate for SCI separately, that management

team would have to feel either very confident or very lucky to go up against a Solution Development company running a three-plex Phase II.

SCII would likely become well known in the SCI community, would have the support of many investigators, and would inspire patients by giving them hope that at least one company has declared all-out war on their condition. Trial recruitment would therefore be easier.

Let’s say that it would take a budget of \$50 million to winnow these half-dozen drug candidates through a development process that included one well-designed three-plex Phase II trial. As long as the people involved with SCII were credible with extensive domain expertise, investors would likely trust them to methodically select a starting set of drug candidates and would then count on cumulative probabilities being favorable that SCII would end up with a compelling drug. Consider that, having bested its peers in development through a proper Phase II that used registration-worthy and commercially relevant endpoints, the winning drug would be much more likely to continue to be successful in subsequent Phase III trials, be approved by FDA and other regulators, be blessed by payors and physicians, and go on to become a blockbuster. Coming out of a multiplexed Phase II program, the winning SCII drug candidate would likely command either a high take-out price or at least win a lucrative partnership from a Big Pharma that has an interest in SCI.

drug(s) eventually get to market. Once the data are generated, all of the compounds could be returned to their originators and the data from the study published and presented. Odds are that the company with the winning drug, assuming it actually beat placebo by a clinically relevant margin, would find it much easier with POC data in hand to attract an acquirer, partner, or investors to fund continued development. Those with the second-rate candidates might still try to massage the results in their favor, but with the full disclosure of the trial results and public knowledge that another drug candidate performed better, it would be harder for them to attract funding to push their candidates forward in that same indication (unless the winner failed in Phase III trials for some molecule-specific reason and the runner-up stepped up to first place).

A ROLE FOR BIG PHARMA

The winner of a non-profit-sponsored multiplexed Phase II trial for an important indication might even be able to attract a

pre-negotiated sale price from Big Pharma. Imagine if a spinal cord injury non-profit were to pre-negotiate with a Big Pharma that it could have an option to acquire the winner of a multiplexed Phase II in exchange for covering the cost of the trial? The non-profit could therefore serve as a catalyst. In fact, a Big Pharma could cut out the non-profit and run its own sponsored multiplexed Phase II trial, leveraging its development expertise to define the criteria by which the candidates and the winner would be selected, and merely providing free entry for qualified candidates and a promise of an option-style deal to reward the best candidate.

Removing the uncertainty of funding and the size of the reward for success would likely mobilize companies and entrepreneurs with early-stage candidates to advance them to the point of being Phase II-ready. That work is relatively affordable compared with the Phase II itself. This would also represent the ultimate culmination of Big Pharma getting out of

early-stage R&D, ceding that part of the process to the supposedly more nimble and clever biotechs. **IV**

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