

Pharmaceutical Industry Readiness for a Phaseless Approach to R&D

... bringing the passion back to R&D

In 2006, after an assignment reviewing discovery databases, the VantagePoint Consulting Group team was able to generalize their findings into an overall picture of the damage being caused by today's fragmented R&D practices: the problem starts right at the beginning in exploratory discovery and stretches all the way through commercial and distribution. Our thinking crystallized at the 2006 DIA during a presentation of Learn-Confirm. We haven't turned back. Many of the conclusions from Learn-Confirm are now seen as a comprehensive fix for pharmaceutical R&D, and commercial's work within R&D.

Productivity in the pharmaceutical industry has at its basis the passion and determination of thousands of highly skilled scientists, clinicians and business managers, laboring in the face of increasing scrutiny, and subjected to increasing skepticism of investors and the general public. It became clear from the beginning of this survey that re-igniting this passion and determination was going to be key for any successful solution to the current productivity gap. The Learn-Confirm approach, in its operational incarnation, addresses many of the issues standing in the way of dramatic increases in R&D productivity. More importantly, the concept sparked the imagination, and soon, the passion of many of the survey participants.

In November of 2006, VantagePoint Consulting Group did an informal poll of several associates about the utility of a Learn-Confirm survey in the industry. We wanted to more tightly hone-in on the key operational features implicated in increased R&D productivity. Any "approach" is only as good as its operational manifestation.

We were guided to several key insights that drove both the survey design and its execution:

- Truly great leaders in R&D are indeed the rarest of commodities, and therefore success depends on us creating an environment where the industry's many good leaders can still thrive.
- Although large firms appeared to be hampered by their size, smaller firms did not seem to have much greater productivity during the late 1990's and early 2000's.
- The Dr. Lewis Sheiner concept of Learn-Confirm was clinically oriented and was very broadly (mis)understood by the industry. Dr. Sheiner should be highly credited for asking the right questions. For the survey, we decided instead to use the term phaseless approach to better express the idea of a continuous, seamless approach to drug development, and to avoid the many connotations of Learn-Confirm in the industry.
- We are also indebted to the writings of Gary Pisano, the Harry E. Figgie, Jr. Professor of Business Administration at Harvard Business School, who decried the "monetization" of biotech R&D as a futile exercise (i.e., counting compounds by phase and applying a risk-adjusted valuation to the portfolio) and explored how to better measure the balance between science and commercial in early R&D.

In short, we were as diligent as possible in rooting out which key operational features would consistently be found in highly productive pharmaceutical R&D organizations and did not "assume" great leadership would just emerge, or productivity would increase by merely changing the size and scope of the operations.

EXECUTIVE SUMMARY

Our research points out the need for greater ownership, responsibility and consequences for early R&D teams - and the need for single-minded attention to the numbers for late R&D. We also investigated areas for improving working relationships with the FDA.

Early R&D

- Pay attention to size and autonomy of the Early R&D organizations. The main objective is to structure an Early R&D organization so that a lean team can effectively manage all the operations.
- The scope of Early R&D organizations should be broad enough to encourage varied scientific pursuits, but within a “design space” that leads to commercial products.
- Concentrate on the knowledge and skills of the staff - they should be among the top in their discipline and should also be well versed in most other Early R&D disciplines. Strive for “implicit knowledge” - staff across multiple disciplines that can talk in shorthand because they’re so familiar with each other’s thinking.
- Ensure the Early R&D organizational structure is consistent with the corporate acquisition strategy. Ideally, a major acquisition will plug into the Early R&D organizational structure with minimal disruption.
- Measure the right things - you’re looking for a balance of commercial and science. Comparing progress across multiple Early R&D organizations can allow for objective assessments of scientific progress.

Late R&D

- Pay attention to standardization and continuous improvement initiatives - for process, systems, protocols and data collection efforts. Factory-like metrics are your most important tool for managing Late R&D.
- Staff Late R&D with individuals in love with harmony, consistency, order, reason and details. Late R&D is not the home for the big or the imaginative thinker.
- Management must focus on holding individuals accountable for concrete, measurable results (either operationally or in areas of continuous improvement).
- Include CRO’s in your overall architecture, planning and implementation efforts.
- Focus on the inputs: a bad clinical plan or protocol will swamp all later efforts at process efficiency.
- Evaluate new technologies solely on their impact on operational efficiencies.

Working with the FDA

- Encourage staff at all levels (not just Regulatory) to get involved with FDA staff at a personal level:
 - Development of global industry standards for system, process and data
 - Early discussions around clinical strategies for new compounds
 - Work on new tools for R&D (biomarkers, adaptive trials, etc.)
- Develop an educational program for all staff to improve their experience in working with the FDA, EMEA and other agencies
 - Understanding the FDA pressures and mindsets
 - Understanding FDA resource constraints and competing priorities

The above recommendations are, as expected, typically greeted with the standard response “we’re already doing that.” However, from the survey it is clear that no one company is doing them all and very few companies are doing any of them well.

EMERGING MODEL FOR EARLY R&D

For purposes of this survey, Early R&D was defined as all activities from exploratory discovery through Proof-of-Concept (POC), including all preclinical and early clinical activities. A precise definition of POC was not given beyond the statement that it involved proving safety and efficacy in hundreds of patients. We did not discuss the detailed assumptions of Learn-Confirm (e.g., use of high variability of early patient populations during the Learn Phase).

Based on the survey findings, the following picture of an Early R&D model emerges:

1. A small, highly autonomous organization (≈200 staff), fully funded, with all the disciplines responsible and accountable for all activities from exploratory discovery through POC, including the execution of clinical trials. Commercial input is embedded and at-the-bench (and has the practical scientific experience to relate market information to the bench).

2. The organization is extremely flat, with a thin management layer mostly concerned with setting the vision, communicating clear goals and objectives, developing business plans, holding staff accountable for achieving the plans, and instituting and maintaining the enabling culture (e.g., embracing dissention, decision-making in the face of ambiguity, breaking down the “knowledge is power” hierarchy, eliminating the “not invented here” syndrome, ensuring a strong understanding of the overall process from exploratory to POC, and embracing new problems as opportunities).
3. Funding for the organization is assured over a multi-year timeframe on the condition that progress is periodically demonstrated. Measures of progress are interim and long-term, as well as commercial and scientific. Consequences of long-term failure are severe.
4. The goals and the objectives of the organization are scoped on a specific scientific platform (e.g., kinase inhibitors), spanning many potential compound classes and clinical targets across multiple years. As in most biotechs today, compounds are not fixed; rather medicinal chemistry (i.e., experimentation) is involved through demonstration of POC. There is no “compound nomination” step in early discovery.
5. The “latest technologies” and a few corporate core competencies (e.g., clinical pharmacology) are available to, but not part of, the autonomous organization.
6. Management encourages personal ownership and hands-on participation in the design, set-up, execution and analysis of all experiments and clinical trials.
7. R&D is “asking a series of questions to make a series of decisions. In many cases though, the best information may not be available until six months later.” One respondent summarized this as the need for industrialization of knowledge acquisition and its incorporation into decision-making. This information can come from within the organization, from across the autonomous organizations, or even from outside the parent corporation (e.g., academia, competitors, agencies).
8. Individuals are encouraged to be the absolute best in their disciplines and are also rewarded for how well they appreciate and work with other disciplines. Day-to-day decision-making is extensively “interdisciplinary”. Rewards are team based.
9. Major acquisitions are set up as additional small, highly autonomous organizations - and are measured alongside other homegrown autonomous organizations.

The single most important decision is to set the initial scope of the autonomous organization, closely followed by the selection of the leadership team.

There was near unanimous agreement on the need to reward decisiveness in decision-making - to get away from decisions on-hold or awaiting more information or from changing decisions (bouncing resources to today’s favorite topic).

A number of respondents emphasized the importance of avoiding “the black swan” syndrome (i.e., “our project must be good [white], because we haven’t seen any bad [black] results”). Respondents called for deliberate and early design of experiments and clinical trials to test the limits of our confidence in any particular hypothesis. This line of reasoning included speeding up First-In-Human at dosages that test efficacy and safety (across many compounds) as the only true test of any hypothesis. Others suggested finding ways to use individual compound “failures” as a means to strengthen the overall scientific hypotheses.

The emerging field of Translations Medicine spans the Early R&D space and can be a natural starting place to achieve this picture of Early R&D. Translational Medicine can partner with the current organizations in Early R&D to provide an overarching strategy for Early R&D. This strategy would encompass the tools, methodologies and platforms for in-vitro, in-vivo and in-human experiments / clinical trials.

“The Translation Medicine line-of-sight is to build the evaluation platform for all molecules from target to POC. The effort would be focused on driving decision-making, well before POC, on the overall approach to get to POC.”

EMERGING MODEL FOR LATE R&D

For purposes of this survey, Late R&D was defined as all activities after Proof-of-Concept (POC) and up to New Drug Application (NDA). This stage is very similar to Dr. Lewis Sheiner's Confirm phase (i.e., Yes-No confirmation, at the scale of a Pivotal Trial, of the hypotheses built into the POC). Most respondents agreed with this model, although a few argued that "learning" continues into the Confirm stage.

Based on the survey findings, the following picture of a highly efficient Late R&D model emerges:

- A global, highly efficient factory, with low-cost, high-throughput operating structures, dedicated to continuous improvement. We have the cheapest, fastest way to get a product to market.
- Management is a rigid hierarchy, with clear goals & objectives, both in terms of daily operational efficiencies and continuous improvement. Key measures are throughput, cost per..., and quality.
- Funding is a combination of infrastructure investment from the corporation and daily operational funding based on the volume of clinical trials. The survey did NOT tease out whether it would be best to have operational funding provided by the Early R&D organizations or by corporate.
- Early in each clinical plan, we are assessing, anticipating and mitigating risk, assessing the likely impact on timelines and regulatory review, estimating the probability of occurrence developing mitigating strategies.
- The goals and objectives of the organization are singularly focused on operational excellence and continuous improvement of the key measures. Clear objectives refer to operational objectives, and not strategic objectives.
- CRO's are integrated into internal systems and processes. CRO staff is rewarded for their contributions to corporate goals of their sponsor.
- Late R&D has access to the latest technologies that bring efficiencies. Examples include running trials over the Internet, good quality compilation and publishing submissions, better means for communicating with investigators and adaptive trials.
- Individuals are rewarded on their contribution to the key measures.

- Processes and systems are standardized across the industry, including standardization of data capture and procedures, as well as standards around the protocol itself.

A few individuals cautioned you must have people in Late R&D who understand Early R&D. Others cautioned that the idea of a lean, global clinical machine is applicable for large companies but not for smaller to medium companies, who must operate on a compound-by-compound basis.

Other respondents emphasized the importance of helping teams make the right leadership decisions, and helping management to understand their needs. A recent successful NDA launch involved some very creative arrangements with the CRO's (structuring arrangements so there's a win-win).

CAUTIONS FOR A PHASELESS APPROACH

Several respondents warned us to NOT set up a concrete barrier at POC - phaseless should be synonymous with seamless even at this crossover point. Pharmaceutical Sciences spans both realms. Clearly biomarkers, models, and even the rationale behind protocols must transcend the barrier. Individuals from Early R&D must stay involved in the Late R&D reviews to provide guidance and understanding of how surrogate and clinical endpoints were derived. "Strive for seamless" instead of "phaseless".

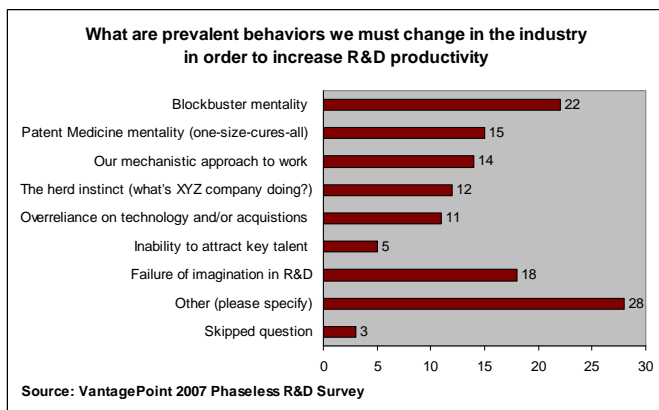
Another respondent pointed out that the industry is a victim of its own successes. That it no longer aims for "bold goals" - preferring safer targets. For example current skittishness about a drug's prospects would have precluded research into statins. There was no consensus that lowering cholesterol was good ... pursuing anti-cholesterol drugs in the early 1990's was a high-risk proposition. The risk-benefit for an Early R&D autonomous organization must allow for the possibility of a long and sometimes tortuous development, including hurdles such as failed trials in related compounds.

MAJOR SURVEY FINDINGS

1. There is a broad consensus across the industry that something different needs to be done – and this consensus is deep, passionate and even angry at times.
2. There is broad consensus that dramatically increased cooperation between the FDA and Industry is not only desirable – from both perspectives – but also critical for a phaseless approach. This cooperation will be deep and broad:
 - New toolkits for development (e.g. biomarkers, models)
 - Joint planning on proprietary compound development strategies
 - Coordination on the emergence of global standards
3. Early R&D is all about the people: we need a fundamental change in the culture and daily work habits of all individuals involved in Early R&D.
4. The change for Early R&D is so fundamental that only an evolutionary approach will work, through the use of pilots, “benchmark” demonstrations, and support of governmental and academic partners. Many respondents also noted the “change fatigue” staff are experiencing in the industry due to the recent waves of change initiatives.
5. Late R&D (from POC to NDA, and beyond) is much more about the organization. What is the best way to organize and measure the Late R&D work to behave much more like a factory?
6. Late R&D process, systems, SOPs, data structures are no longer viewed as Intellectual Property and can be standardized globally for the industry.

SURVEY FINDINGS

Finding 1



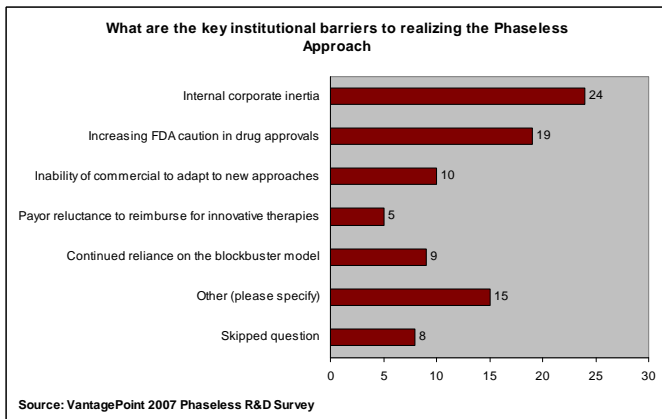
Although most individuals selected “Blockbuster Mentality” as a key behavior that needed to change, there was little discussion on the rationale for this selection other than “the rise of personalized medicines” or “profitable markets in the sub-blockbuster arena.”

The “herd instinct” combined with “failure of imagination” in new ways to operate were by far the key behaviors that respondents felt needed to change, and were able to be changed.

Respondents mentioned that many individuals prefer a cookie-cutter approach when dealing with their daily work habits. Individuals in the industry have a very high fear of failure, which is regularly reinforced with any small mistake. So individuals tend to stay with their tried and true work habits.

This “herd instinct” also extends to the selection of drug targets - with the industry only tending to focus on “druggable” targets. Several individuals lamented the lack of bold goals and objectives for the industry.

Finding 2



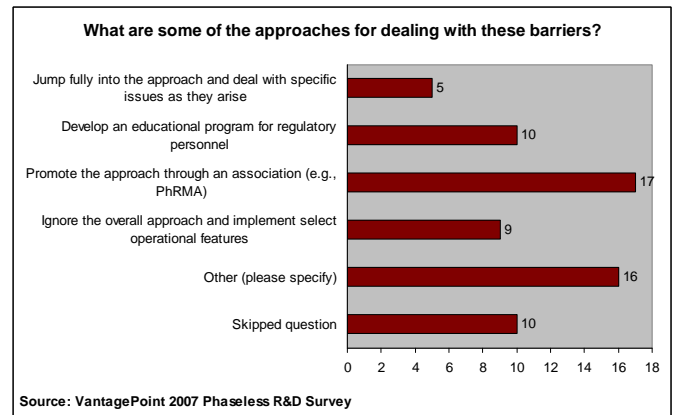
Internal corporate inertia was by far the most frequently cited reason for not realizing a phaseless approach. Our probing of this response revealed a mixture of cultural bias and corporate inertia. Many times, the “academic” culture in Early R&D was the barrier and not a lack of efforts by many well-intentioned individuals. Others mentioned “the safety trump card” used by many individuals to halt operational improvements.

Selection of “Increasing FDA Caution ...” was due mainly to today’s environment, with several major products recalled from the market. Several individuals mentioned that this was not a “barrier”, merely a reality of drug development that we needed to face up to.

The multiple-choice answer “Payor Reluctance to Reimburse for Innovative Therapies” elicited a broad range of responses. Some felt that payors were quick to “pull out the old morbidity and mortality card”, stifling innovation. Others felt that payers would pay a premium for any significant product differentiation but that “good contracting arrangements by commercial” could swamp a 2% differentiation in a surrogate endpoint. In either case, there was general acknowledgement that this was the new environment in which the industry must operate.

Several respondents mentioned that the risk-benefit analysis is NOT a hard science, that it will always contain lots of subjectivity. So it is not unusual for drugs with lots of benefits to lots of people to be overwhelmed by significant risk to a small number of individuals. Several respondents lamented the end of most efforts at “preventative medicine” due to this very concern.

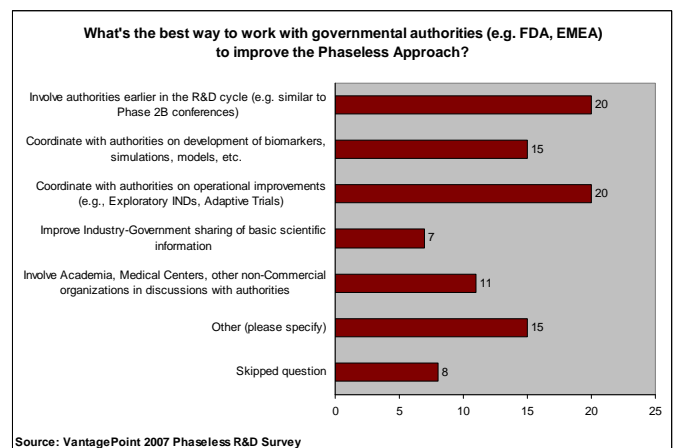
Finding 3



The majority of respondents (from industry) preferred to start with a prototype or pilot of the phaseless approach (Multiple-Choice = Other). Many felt that getting academia and/or an association involved, and having them set up and test alternate operational models, would speed the introduction of the approach. Respondents from smaller companies refused to even consider the approach in the absence of FDA sanctioning the approach.

Several respondents cautioned against “one size fits all” - both from the therapeutic area and from the size-type of company. Most respondents recommended an intense education program for many of the Early R&D participants to help reduce the many cultural barriers identified later in the survey.

Finding 4



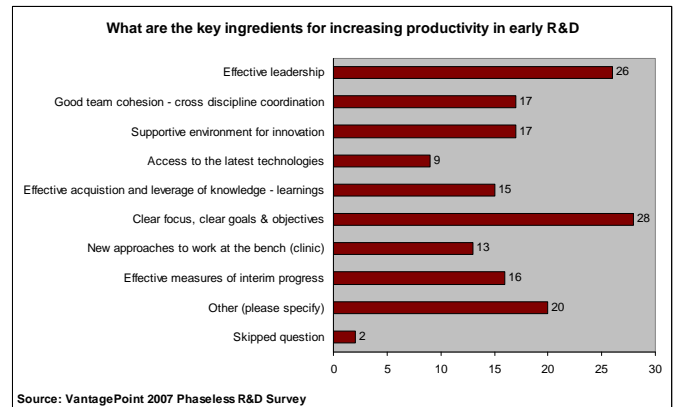
Most respondents agreed that working closer and more frequently with the FDA could greatly increase the productivity of the industry and enable the Phaseless approach.

This working collaboration could cover several areas (as hinted by the multiple-choice answers):

- Working together on novel approaches (e.g., adaptive designs, seamless designs)
- Using the FDA (or a consortium) as a “clearinghouse” for sharing of non-proprietary information (e.g., toxicology and placebo databases, animal models, biomarkers, disease frameworks, patient populations, disease homogeneity)
- Leveraging the influence of the FDA to promote global standardization of systems, processes, data structures (even demographic protocol fields for CRFs)
- Industry support of an educational program for FDA reviews and for industry staff who interact heavily with FDA.

A few respondents (from industry) mentioned disappointments from prior FDA-industry initiatives. A few respondents from the FDA mentioned disappointment with industry timidity in dealing with the FDA.

Finding 5



This was the most discussed topic in the entire survey. Many respondents pointed to the high level of failures of Phase 2B compounds (which they equated with POC) and felt that this was the most pressing issue to address in the industry.

Leadership and Clear Goals & Objectives garnered the highest number of responses. As can be seen in the quantitative results, most respondents selected most of the multiple-choice answers.

Our analysis of this question therefore relies heavily on the telephone interviews that followed the online survey responses. There were many key topics discussed for Early R&D, shown in the table below.

Early R&D Key Topics 1(4)

Impact of Acquisitions

This topic was frequently mentioned, either in a highly negative connotation, or in a “savior” connotation. Several respondents, typically those closest to Early R&D work, riled target acquisitions as detrimental to Early R&D morale and productivity. “Folks get the attitude that the science they do doesn’t matter, because management will just make another acquisition anyway.”

On the other hand, several respondents, typically those outside of the Early R&D (or working for smaller companies), felt acquisitions should be an integral part of Early R&D for “big pharma”. Basic science could be better nurtured outside of “big pharma” in certain therapeutic areas (e.g., oncology). Others felt the basic science should be performed outside of industry and that industry should only be responsible for taking the basic science and turning it into products.

A few individuals use acquisitions to “shake up the status quo” - acquisitions have higher hurdles for entry and yet are more quickly discontinued because of negative results. “Learnings” from acquisitions frequently inform further science and development.

Early R&D Key Topics 2(4)

Cross-Discipline Coordination

Many respondents agreed that teams were too myopic in their particular disciplines and that what was needed was consistency of vision from the cellular level to disease outcome in man. Proposals ranged from rotational exposure of scientists to forcing greater involvement of all staff from the beginning (i.e., Exploratory, Discovery), to harmonizing protocols, methods and analytical rigor from in-vitro to in-vivo to in-human.

Although cross-discipline sharing was broadly acknowledged as a key ingredient, some respondents sounded a cautionary note that we need to be careful NOT to weaken core disciplinary skills as part of our drive to increase cross-disciplinary understanding.

Cultural Barriers

By far the most frequently mentioned issue, and the ingredient that will take the longest to address, is the need for cultural change. Many scientists, clinicians, MDs, and others come to industry with an academic approach that manifests itself in several ways:

- Not accustomed to “disproving hypotheses” as a matter-of-course
- Low “tolerance for ambiguity” in decision-making. “Our motto is we should be working with reasonable rather than perfect knowledge.”
- Not accustomed to thinking about the entire process rather than their individual contribution
- Preference for a deterministic / mechanistic approach to work - rather than a systemic view of how all the work fits together
- Unwillingness to “be on the critical path” - to deliberately slow down a project when they have doubts
- Failing to recognize “problems” as opportunities - either for learning or for setting up hurdles for the competition through patent-protection
- Small view of the world - agonizing about thousand dollar investments when the most valuable assets are their concentration and time

Of course, many of these cultural barriers contribute to a lack of decisiveness in decision-making.

Decisive Decision-Making

There was almost unanimous acclamation that the inability to make decisions is the most detrimental organizational behavior in Early R&D. Most expressed this concern in relation to the inability to kill bad compounds. However, the context is valid for any Early R&D decision-making. Some recommendations for improving decision-making in Early R&D include:

- A clear vision (Goals & Objectives) is critical to good decision-making. For example, clarity around which elements of the Proof-of-Concept are most critical (i.e., show-stoppers). Clarity around which elements of the Protocols are most critical (i.e., avoid “wish lists”)
- Decision-making tends towards “only making safe decisions” as organizations become larger, so keep organizational units small
- Incentives should balance the making of decisions, along with the decisions made (e.g., tiered incentive schemes, independent decision makers)
- Many respondents felt they could better organize and improve processes to force a strong decision-making culture

Decision-making is closely tied with comments made on incentives.

Early R&D Key Topics 3(4)

Scope

Several individuals, especially if they were familiar with the goals of Translational Medicine, emphasized the need to move away from a “compound focus” in Early R&D. “Other industries have a continuous improvement model [of product development] ... they can go to a second technology. We need ... assessments to improve the molecule ... for example, [today] it’s practically impossible to derail a compound in favor of a better one in back of it.” This maybe a way of organizing the work in Early R&D to achieve a proper balance between scientific and commercial interests.

Early R&D, from Exploratory Discovery to POC, is all “experiment” was the sentiment expressed by one respondent (Head of Discovery). This recognized that in-vitro, in-vivo and in-human testing shared many similarities and that “experimentation” isn’t proven until proven in humans.

Several individuals from Translational Medicine emphasized the “platform” or the “evidence trail” - the collection of experimental results that takes a reviewer from the cellular target to the clinical outcome. Several respondents, although understanding the importance of the platform, cautioned that POC must include commercial input. POC must provide the desired clinical outcome and not just some surrogate measure (e.g., reducing cardiac events as a result of lowering cholesterol).

Use of Incentives

Closely related to decision-making were the reward structures for Early R&D. All recognized the overwhelming importance of getting this ingredient right. Most emphasized the need for team-based incentives. Many recognized the need for managers to be rewarded on their ability to properly motivate staff and to hold them accountable. Accountability (and consequences) was brought up by many of the respondents.

Role of Metrics

Related to incentives, many respondents recognized the importance of closely linking incentives to metrics. Many respondents provided examples of the misuse of metrics. “Pharmaceutical R&D is the only operation in the world where the individuals being measured are allowed to collect and report their own results.”

Most respondents agreed on the need for interim measures (it’s a long time between POC’s), but only a few examples were offered. Some respondents felt that counts of POC’s could serve as the final measure but with the caution that this must include a commercial assessment of each POC (i.e., not a POC unless commercial considers it worthy of moving into Late R&D).

A couple of respondents attempted to address the idea of using a Venture Capitalist model to measure interim progress: i.e., comparing progress across a portfolio of mini-organizations, dropping the underachievers, and adding new mini-organizations on a regular basis. There is still the difficulty of trying to determine “what to measure” when comparing across mini-organizations (i.e., how do we judge scientific progress without stifling innovation).

Team Sizes

Many respondents mentioned that big pharma is “just too big” - that early development is not as scaleable as you might think. Managers spend too much time and frequency in reviews and too little time on assessing the quality of the science.

Several respondents identified GSK’s Centres for Excellence in Drug Development (CEDD) as an intriguing model: breaking early R&D into smaller units that are defiantly independent. Others pointed out the danger of simply replicating the problems of large pharma many times over in the smaller CEDDs.

A few respondents addressed the questions of key ingredients for smaller scale organizations: key individual(s) with a compelling vision and investors who share that vision.

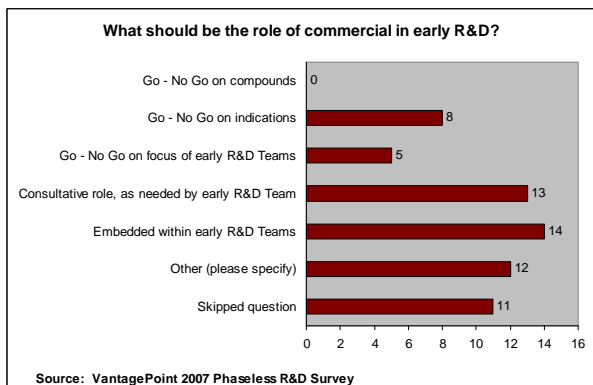
Early R&D Key Topics 4(4)

Use of Technology

Early in the survey, several individuals (mostly in academia associations and in small companies) pointed to the large investments made by the industry in Early R&D technologies over the last 10 - 15 years with no impact on R&D productivity. “Industry became too enamored by the genome phenomena, robotics, the millions of compounds screened ...” An early consensus in the survey was that there was an over-reliance on technology, to the detriment of the basic, hands-on science. “It’s nice that sequencing machines can do thousands of compounds in a week ... but if it takes a few more days to do it by hand, that’s too bad.”

As the survey progressed and the issue further pursued, other individuals were less certain, citing the long lead times, fundamental process changes, and steep learning curves required to make these technologies work. By the conclusion of the survey, a more balanced consensus was achieved: technologies were useful as shared activities across domains, but only if management provides clear direction.

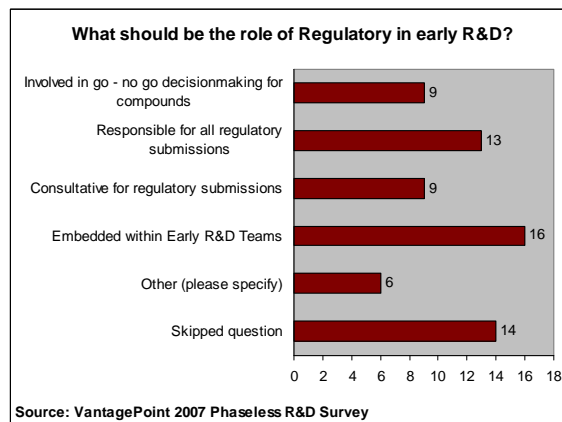
Finding 6



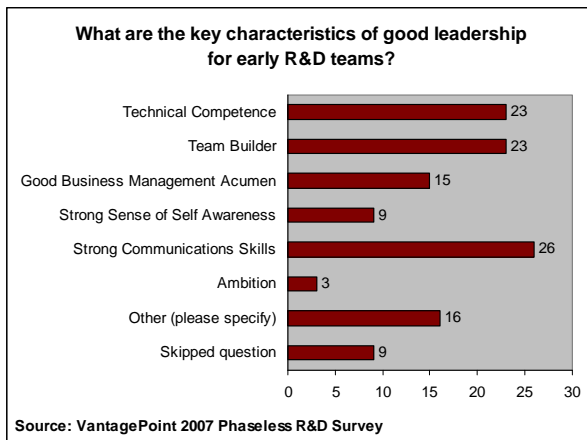
Responses were evenly split between embedded and consultative with little differentiation by respondent based on function or type-size of organization. Probing the issue during the telephone interviews suggests the preference is strongly influenced by personal experiences with good and/or bad commercial staff.

Although we did not collect the quantitative numbers it does appear from the ambivalence in many responses that high-quality commercial representation would be welcomed as a valuable team member in Early R&D, even at the bench level (all the way back to exploratory discovery). Several respondents supplied their definition of “high-quality”.

Finding 7



Responses slightly favored embedded within Early R&D Teams. Respondents from regulatory-related disciplines tended to favor the more embedded role. Most respondents felt that regulatory would be responsible for all submissions and FDA interactions, but as a representative of the scientists. There was not a lot of debate on this topic.

Finding 8

The most important characteristic was good communication skills, especially the ability to take complex information and to simplify the information into a concise message for the team. This is closely related to being a good “team builder”.

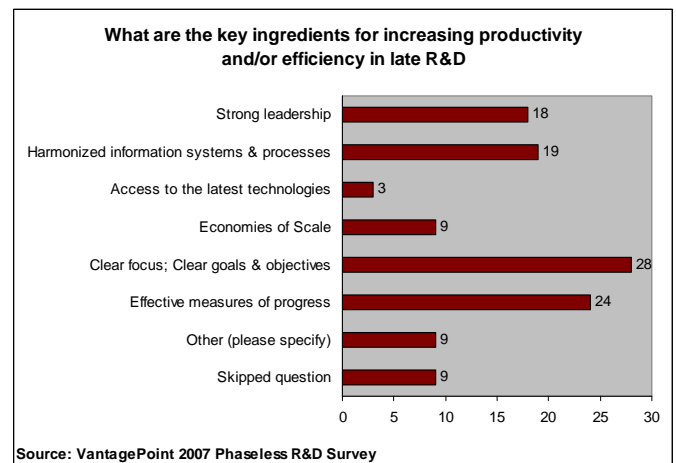
Although most respondents selected “Technical Competence”, our telephone interviews revealed a wide divergence in what this would constitute. The majority defined it as having a practical knowledge (hands-on) of the end-to-end process (from Exploratory through POC). A few defined it as discipline expertise (the MD-PhD); others defined it as changing disciplines in the lead as projects progress.

Ambition, in its selfish form, was only selected by a few, as a necessary evil.

This question elicited the most substantial responses to “other”:

- Hold individuals accountable
- Makes decisions
- Charismatic
- Able to read people
- High emotional intelligence
- Influence individuals that are not direct reports
- Teacher
- Embraces problems
- Knows when to be on the critical path

Several respondents mentioned that truly great R&D leaders have historically been very rare and that management’s top job is to find the next great leader. During the telephone interview this idea was discussed, and the respondents were encouraged to define the supporting environment that would make merely “good” leaders highly productive (hence the lengthy responses to the question on Increasing Productivity in Early R&D).

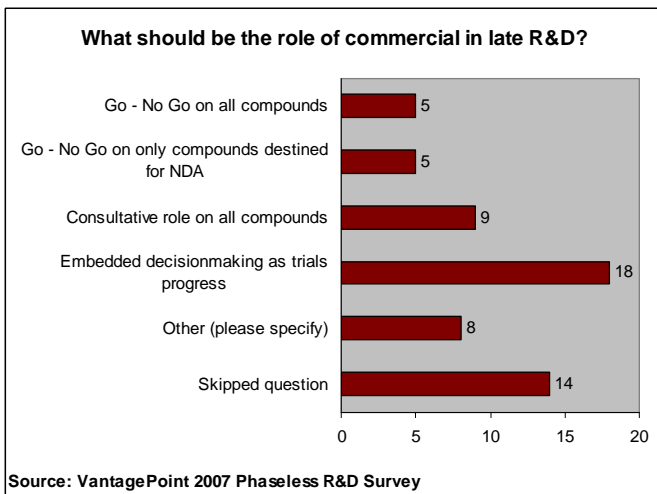
Finding 9

Clear Goals & Objectives was the most selected response, with the “leadership” to enforce those goals and objectives as the second most selected response. Most respondents strongly believed Late R&D should be more “factory like” or “heads-down” execution of the work.

Given the “factory” analogy, most respondents agreed that strong process improvement metrics were essential (e.g., cycled time, throughput). Also, there was nearly universal agreement that processes and systems were NO LONGER proprietary to individual companies. There was nearly universal support for industry standards on systems, processes, date and even “>70% of protocol elements”. This standardization “should be well beyond the current efforts of CDISC.org and CRIX.nci.nih.gov.”

A few respondents felt that the “Learning” continues into Late R&D. The survey did NOT probe how this “learning” would avoid “the patent medicine” approach to R&D.

Finding 10

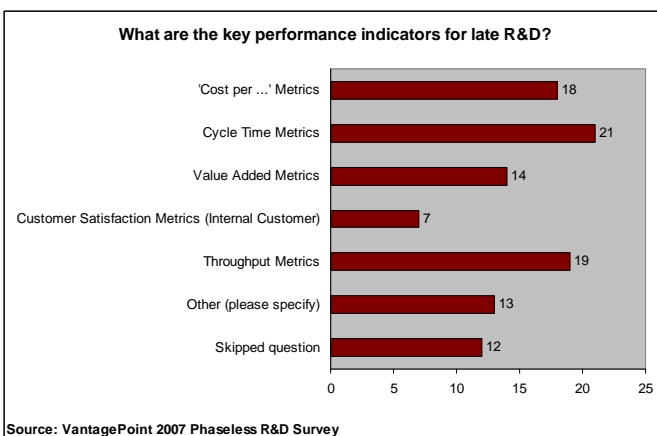


Different from Early R&D, there was a strong preference for having Commercial Embedded in Late R&D.

Most respondents, when questioned, did NOT want commercial second-guessing the R&D program, rather wanted R&D folks providing options, with Commercial selecting from among the options.

One individual, near the end of the survey, lamented the fact that commercial is more reticent in “preparing the marketplace in advance of a launch” - referring to the 1990’s Merck development of the cholesterol marketplace in advance of the launch of Mevacor.

Finding 11



Most respondents identified “process metrics” as key to controlling Late R&D. As a “strategic” process metric,

one respondent mentioned his organization (clinical operations) aimed in 2-3 years to not have any of his staff reviewing protocols (they should come out of Early R&D without any need for further review). As “operational” process metrics, most respondents mentioned “cycle time”, “throughput” and “cost per ...” metrics.

Some respondents mentioned that by Late R&D, “everything is pretty much locked in” ... that if you don’t have the clinical plan well defined before starting in Late R&D, then process metrics will probably only have a minimal impact, ... “We measure cycle time because we can.”

Several respondents identified a need to capture “goal metrics” ... the “value” of the compounds to the patients - payors. “A lot of effort is being put into this area.” The key metric, the most important metric, is “how we demonstrate we add value to the folks that’ll buy our products”.

Many respondents cautioned that metrics are only as good as how they’re used ... and described the many abuses of metrics they have seen. Several respondents mentioned that metrics are NOT tied to incentives and therefore become just an exercise in futility.

Other respondents mentioned the difficulty in collecting base information for metrics. At best their metrics are a cut-and-paste operation. Management-by-exception is NOT yet possible because of the unreliability of the metrics.

CONCLUSIONS

It was clear from the passion in the responses from many of our survey participants that the pharmaceutical industry is anxious for a new approach to R&D. However, most acknowledge the need for some basic operational capabilities before moving to the phaseless approach (i.e., crawl before you walk). There are notable gaps in the industry around Early R&D culture and decision-making.

Also, our survey uncovered the need for further investigation into several other areas. There was little appreciation for sources of innovation in science or for leveraging of knowledge across the competition. One respondent noted: “It will be very difficult to get the pharmaceutical industry to set up a trading scheme for basic scientific knowledge, even if it is the right thing to do.”

Despite prompting during many of the telephone interviews, it became apparent most respondents had great difficulty in surmounting their bias towards counting compounds in Early R&D. They tended to view the molecule as a physical manifestation of their work, and they continued to search for better ways to “monetize” Early R&D.

Going forward, much of the preliminary work in Early R&D must be around basic operational competencies needed before moving to a phaseless approach:

- Developing inter-disciplinary work practices and incentives
- Viewing basic science as fungible and readily tradable for more basic science
- Incorporating Translational Medicine insights into daily work practices
- Identifying key measures of success and how they relate to drivers of success

In short, we need to establish an operating environment where individuals are so driven toward a common vision, and so connected in their thinking, that all the other concerns of today fade in significance.

The basic operational competencies for Late R&D are much clearer (at least to a management consultant):

- Designing and documenting the overall processes and system architecture
- Developing and enforcing standards, starting with an overall architecture.
- Developing and enforcing metrics, including linking of metrics to rewards
- Designing and building the working relationship with CRO’s, with joint rewards and penalties for performance

Late R&D is in the purview of the “Operational Efficiency” experts and is an ideal target for Six Sigma techniques. The obstacles are significant, but the rewards are enormous.

THANK YOU

We would like to thank all those individuals who took valuable time from their “day jobs” to share their insights and passions with us for this survey. We also thank the individuals who attempted to participate in the survey, but for very understandable reasons were unable to contribute.

METHODOLOGY

The data for this report was collected, with global participation, using an online questionnaire with 12 multiple-choice questions. Participants were not required to force rank choices and could select as many choices as they deemed appropriate. All questions included “other”, which most participants used liberally to further explain their multiple-choice selections. The survey was divided into 3 sections:

- Problem Definition
- Early R&D
- Late R&D

The online survey was followed by a telephone interview, which typically lasted 40 minutes. The telephone interview probed in-depth the areas of expertise for passion of the participant (i.e. not all questions were probed equally with all participants). Many times, participants were asked why they did NOT select certain multiple-choice answers in order to better understand their reasoning.

Participants were invited to the survey using a “referral” methodology. None of the participants was more than 3 degrees separated from the key survey personnel. Only one participant was a “cold call”. Most participants were at 2 degrees of separation. All responses were and will be kept confidential, both as to the name of the respondent as well as the names of the companies represented.

The survey was designed to get as varied participation as possible. A review of the Participation Breakdown, below, will show that we succeeded, with the exception that the survey ended up being more weighted toward senior management (i.e. very few bench scientist participated).

PARTICIPATION BREAKDOWN***By Organization:***

- Size
 - Large (6)
 - Small- Medium (6)
 - Other (4)
- Industry
 - Biotech (4)
 - Small Molecule (8)
 - Other (4)
- Location
 - Asia-Pacific (2)
 - Europe (4)
 - United States (10)

Department:

- Academic Affairs
- Planning & Quality
- Commercial Operations
- Research & Development
- Translational Medicine
- Pharmacology & Toxicology
- CEO
- Regulatory
- Biostatistics
- Biomarker Development
- Development Operations
- Phase 1 & 2 Development
- Global Site Services
- Project Management
- Scientific Affairs
- Chief Science Officer
- Methodology Innovation
- Licensing & Acquisitions
- Clinical Operations Strategy
- CIO, R&D
- R&D Finance
- Medical Policy
- Head of the School of Pharmacy
- Discovery
- Noted Author
- Development, Cardiovascular
- Biomarker Innovation
- Clinical Quality Systems Integration
- Clinical Research Administration
- Clinical Research, Clinical Pharmacology
- Clinical Research, Experimental Medicine
- Neuroscience Global Medical Operations

Management Level:

- Associate Director (2)
- CEO (1)
- CIO (1)
- Director (5)
- Executive Director (7)
- Executive Vice President (2)
- Global Director (1)
- Senior Pharmacist (1)
- Senior Scientist (1)
- Senior Vice President (6)
- Vice President (13)
- Head of ... (1)
- Senior Director (1)

Forty-three individuals took the online survey. One individual was anonymous. Thirty-nine of the forty-three individuals took both the online survey and the telephone interview.

VantagePoint Consulting Group performed all data collection and analysis. The intent of the online data collection was NOT to develop statistically significant responses but rather to help us identify areas of expertise and/or passion of the participant for further discussion during the telephone interviews.

VANTAGEPOINT CONSULTING GROUP

VantagePoint Consulting Group is a leader in providing clients strategic, operational and technology solutions to address their most pressing needs. Our staff has decades of management consulting experience, and a history of delivering results that work. Based on our deep expertise in Pharmaceutical R&D, we feel comfortable in supporting the industry trend towards a Learn-Confirm approach to R&D. Different companies have tailored this approach to their own specific needs. Looking across many companies, we provide an industry-wide perspective on implementing Learn-Confirm.

CONTACT INFORMATION

Keith Ortiz

Partner

(908) 788-7350

KOrtiz@vantageptconsult.com

Marsha Montgomery

Principal Consultant

(908) 788-7350

MMontgomery@vantageptconsult.com

BY

Keith Ortiz

KOrtiz@vantageptconsult.com

SPECIAL THANKS TO

Marsha Montgomery

Toni Cantalupo

Leslie Hammesfahr