DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(1&2), 277-294 (1993)

PHARMACEUTICAL DEVELOPMENT: PRESENT AND FUTURE DIRECTIONS*

D. C. Monkhouse and W. A. Valinski
SmithKline Beecham Pharmaceuticals
Research and Development, Pharmaceutical Sciences, UW2217
709 Swedeland Road, King of Prussia, PA 19406

ABSTRACT

The future of Industrial Pharmaceutical Sciences depends upon an objective evaluation of the discipline in light of recent changes in the marketplace, the industry, the nature of new chemical entities entering the pipeline, manufacturing technologies, worldwide regulatory requirements, and even the plight of Academic Pharmaceutical Sciences. A proactive agenda must be established to effectively harness the business of Pharmaceutical Development to then drive interdepartmental alliances within R&D as well as with Commercial Manufacturing and Marketing. Pharmaceutical Development groups must become well integrated, dynamic learning organizations that can enhance the ability of Industrial Pharmaceutical Sciences to advance its unique, yet diverse science towards the twenty-first century.

---

* Presented to the Pharmaceutical Manufacturers Association's Pharmaceutical Development Subsection (PDS) Annual Meeting on 07 April 1992 in Washington, D. C.

INTRODUCTION

How Industrial Pharmaceutical Scientists will be able to continue to develop the discipline and apply its unique, yet diverse science will become increasingly dependent upon how Pharmaceutical Development conducts business in a complex global environment. To address the "challenge of excellence" in Industrial Pharmaceutics, members of the discipline must examine Industrial Pharmaceutics with the same zeal with which Academic Pharmaceutics was recently evaluated[1]. The industrial terrain and the regulatory milieux have changed considerably, yet the discipline as such has been slow to respond. More aggressive tactics and a clearly-defined strategic intent for the discipline are critical to the survival of Pharmaceutical Development as a scientific pursuit in the drug industry.

HISTORICAL PERSPECTIVE

The global pharmaceutical environment is changing swiftly. The pharmaceutical giants created in the 1970s and early 1980s nearly doubled in size since that time as a result of over a decade of mergers and acquisitions. The list of examples is seemingly endless including Warner-Lambert-Parke Davis, Bristol Meyers-Squibb, Marion Merrell-Dow, Rhône-Poulenc Rorer, and Smith Kline & Beckman which has since become SmithKline Beecham. Many mergers logically occurred between corporations which were based in different countries and had non-overlapping product portfolios thus providing entrance into different country or local markets. By intentional design, these merged corporations became increasingly transnational to address a worldwide marketplace.

Many of the newly established pharmaceutical giants, like the discount store K Mart, took a textbook approach to management by centralizing business operations, manufacturing, and distribution practices[2]. Unfortunately, such a

traditional approach to the creation of megacorporations may be impotent in addressing an industry which is in tremendous transition technologically, financially, organizationally, and legally. Clearly, the products in the pharmaceutical pipeline are becoming more complex. The financial risks of Pharmaceutical Development are greater today and the return on investment is smaller. Regulatory agencies are also becoming more and more aggressive. The FDA is getting tougher, but it may soon be outdistanced by health authorities within the European Community, Canada, and Australia.

Although corporate mergers and acquisitions are still occurring in the pharmaceutical industry, the frequency of such events may be decreasing. The 1990s may become the decade of strategic alliances and joint-ventures, such as Dupont-Merck and Rhône-Poulenc Rorer/Chugai[3]. The decreased momentum towards *merger mania* may be because such practices have not produced the expected results. The number of new chemical entities (NCEs) per R&D dollar may not have been enhanced by corporation size as suggested by the results from a recent 19-year study of 31 firms[4]. Notably, the giants of other industries also have uncertain futures. Companies such as "Kellogg, Rank Xerox, Kodak, Black & Decker, Rubbermaid" suggest that increased corporate size may not necessarily be better. Large corporations are like elephants, difficult to move[5].

RESPONDING TO A DYNAMIC MARKETPLACE

Competitive advantage is often short-lived. Big companies having a clear competitive edge in one year may be struggling for survival in the next. IBM is only one in a series of potential examples. The inability to predict who will come out on top makes it difficult to find appropriate corporate models to emulate. The dynamic nature of the marketplace may mean that competitive imitation is not the answer. The "perfect drug company" is being constantly redefined. Corporations must look beyond today's marketplace and anticipate

tomorrow's market. The newer generation of corporate agreements may necessarily become more product or process-specific providing for a more restrained means of expanding or managing an already established drug portfolio. Another change in corporate behavior is suggested by the continued practice of in-licensing and out-licensing of products. Such changes in the industrial terrain have a major impact on the management of established drug portfolios by Pharmaceutical Development groups.

To excel or even to survive, a tenuous balance must be established between working with current capabilities (tactics) and envisioning the corporation of tomorrow (strategy). Yet, a corporation can only compete on its current capabilities[2]. Pharmaceutical Development along with the rest of the organization must implement continuous improvements which are clearly results-driven[6] and also linked to strategic intent[7]. To accomplish this, upper management in Pharmaceutical Development needs to capture the "essence of winning" and instill it in personnel at all levels[7]. A compliant staff is no longer enough; a committed, continuously learning organization is the *sine qua non* of effective competition. Workers must identify Pharmaceutical Development's success with their own[8].

Clearly, successful competition in the pharmaceutical industry in previous decades does not necessarily mean continued success. Though bigger may have been better at one time, evidence is mounting that it may not necessarily be better in the 1990s. Many smaller newer companies are successfully championing high risk niche markets. In the past, the industry could invest strongly in Discovery because patent protection and exclusive franchises of potential therapeutic niches allowed for long development times for products targeted to a homogeneous customer population of physicians who prescribed to a largely insured population.

TRADITIONAL COMPETITION - THROUGH DISCOVERY

Successful competition in the 1990s is complicated by shortened patent protection as a result of generics, less of a monopoly on scientific knowledge,

and a shorter discovery time due to mass receptor screening of drugs and the cloning of receptor subtypes. The market is also typified by a diverse customer population, including third parties, cost-containments, and a greater personal choice. The result of these and other factors has been a smaller financial return on investment. "Of the 512 new chemical entities launched internationally between 1979 and 1988, only 25% managed to achieve sales of US$25 million a year... the remaining 75% are unlikely to have recouped their R&D investment."[9] A reexamination of the ability of Discovery to continuously provide a competitive edge is necessary. Perhaps, a strategic investment in Pharmaceutical Development as well may enhance an organization's competitive ability.

The ability of Discovery to determine competitive advantage is constrained by recent advances in scientific research. Though traditional Pharmacology[10], in conjunction with Medicinal Chemistry[11], is the primary arena for the discovery of medicinals, fewer compound classes are available for exploitation, despite the characterization of receptor subclasses. Most large pharmaceutical companies are examining the same groups of receptors, ion channels, and growth factors. Molecular Biology has merely accelerated the pace of Discovery by allowing for more discriminating screenings assays. Monoclonal antibodies have become "magic bullets"[12] that effectively compress the Discovery window. Perhaps the area of natural products is still a wild card for Discovery; it may be where Discovery is still the driving force for the successful introduction of such natural products as Taxol. Even in such cases, however, Pharmaceutical Development may be the yet unrecognized critical partner to successful competition.

DYNAMIC PRODUCT PORTFOLIOS

Project portfolios are largely the logical result of Discovery's emphasis. Advances in biotechnology have clearly accelerated the pace of Discovery;

biotechnology has also transformed Pharmaceutical Development in some areas. The number of biotechnology patents has increased since 1985[13]. The products most affected are diagnostics, but vaccines, antineoplastics, and antivirals more often utilize biological processes[13]. Product portfolios have the added caveat of product introductions and terminations via in-licensing and out-licensing as well as the impact of competitive product lines that makes the dynamic terrain of Pharmaceutical Development ever changing. An NCE which is second in the race at one time may be in the lead when a competitors' compound unexpectedly drops out of the race.

Because Discovery time is compressed, "time has emerged as an increasingly important factor in producing a successful drug portfolio"[14]. Consequently, it is becoming critical that Pharmaceutical Development be strategically advanced. In a corporate world of limited resources, *ad hoc* Development is no longer feasible. Industrial Pharmaceutical Scientists must work smarter, as they are already working harder than ever. Traditional competition must be transformed into time-based competition[14]. Pharmaceutical Development must strategically advance an ever-changing portfolio of new products, growth products, and mature products. Being the first to market a product for an untapped therapeutic niche is clearly lucrative. Proactive management of growth and in-line products is also essential to achieving a "balanced scorecard" necessary to "drive performance"[15]. Corporations such as Hewlett-Packard, Cannon, and Sony have successfully transformed seemingly mature products into a new generation of growth products which have provided a tremendous return on investment to their corporations and a better product to their customers[16].

ENHANCED COMPETITION - THROUGH DEVELOPMENT

The ability of Pharmaceutical Development to proactively help its parent organization to acquire and maintain a competitive edge is hampered by a severe shortage of Academic Pharmaceutical Scientists[1]. The reasons why

Pharmaceutical Development has been unable to drive R&D and make Pharmacy issues an integral part of the project planning process are numerous: academic prestige does not match that of Discovery fields, limited grant support has forced an exodus from academia to industry, fewer research departments train the next generation of professionals, necessary training must be conducted on-the-job, and the lack of trained researchers has led to non-traditional hires requiring even more on-the-job training[1].

Though Academic Pharmaceutical Scientists have been driven to industry, the discipline is constrained herein. Competition for the limited number of trained Pharmaceutical Scientists to support industry is fierce. Like the rest of R&D, Development is also forced to operate with limited personnel and resources while having to accommodate an increasingly diverse and complex product line. Because Pharmaceutical Development is largely project-driven, there is little institutional sympathy for the time it takes to formulate, analyze, and manufacture elegant drug products. Rewards for a job well done are rarely directed to Industrial Pharmaceutical Scientists. Pharmaceutical Development is a mystery to much of the organization and is, by default, perceived as the rate-limiting step to new product introduction. Like Rodney Dangerfield, Pharmaceutical Development frequently gets "no respect" from much of the organization.

INTERNAL MANAGEMENT STRUCTURES

For Pharmaceutical Development to enhance its collaborations with other areas of the corporation, however, a reexamination of how Industrial Pharmaceutical Scientists do business internally is necessary. Many Pharmaceutical Development organizations have adopted some form of matrix management, yet the efficiency of cross-functional teams is difficult to measure. Some would even contend that the experiment of matrix management is a clear management failure[16]. Though matrix management allows for individual

originality and group creativity, it also may lead to diverse decision making, inefficient meetings, and tactical, not strategic, decisions. Conversely, line management is characterized by clear accountability, localized decision making, fewer meetings, and strategic decisions. Yet, the effectiveness of line management in a diverse field such as Industrial Pharmaceutical Sciences is questionable. The discipline needs to successfully change or integrate matrix and line management[6] to become an integral part of the competitive process. Internal strategic alliances between line management and matrices within Pharmaceutical Development must empower cross-functional action teams and make decisions more strategic. Current tactics need to be linked continuously to the strategic intent outlined in initial development plans to proactively minimize crisis management.

Creating and Managing Action Teams:

Action teams are groups of scientists consisting of formulators, analysts, and manufacturing scientists who are devoted to the development of a single product or family of products. Such groups are not, however, "a few bright people in a dark room, [with] some money, and hope that something wonderful will happen.[6]" Action teams must be empowered to effect change that is both results-driven and with a view to the future. Management must provide action teams with training in total quality management (TQM), statistical tools, and continuous reinforcement of the groups' mission. "Employees [should] receive training in various analytical techniques, team-building.. [to] achieve goals more quickly; teams [should be] introduced [to] performance measurements as... needed; and managers [should] analyze and redesign work processes. Innovation [should be] introduced only if [it] contribute[s] to the realization of short-term goals."[6]. Pharmaceutical Development and innovation are necessarily directed and occasionally supplemented by "expert systems"[17] when individual expertise or experience is lacking. Overall, strategic decision making and innovation should be strongly rewarded[16]. The head of a

Pharmaceutical Development group must mobilize staff from the top down to execute a strategic plan to achieve a strongly stated mission[5].

INTERNAL STRATEGIC ALLIANCES

Internal business exchanges between Pharmaceutical Development and the rest of R&D as well as Commercial Manufacturing and Marketing are typically one-sided and driven by internal customers within the corporation. Like corporations as a whole, Pharmaceutical Development needs to gain control over its business and redefine the role of the discipline in the pharmaceutical industry. Clearly, Pharmaceutical Development is one of many R&D groups that provides services to a large segment of the corporation[18]. A reexamination of how business is conducted during these exchanges is necessary. Pharmaceutical Development needs to optimize synergies between departments to best utilize available resources, to minimize boundaries between groups, and to provide a mutual understanding of one anothers' problems and progress. Unfortunately, the organization needs to learn what Pharmaceutical Development does before it can consider it an integral, equal partner. The diversity of expertise and technical challenges unique to Industrial Pharmaceutical Sciences must be expressed to the breadth of the organization.

Organizational Hierarchies:

The role of Pharmaceutical Development in the organizational hierarchy needs to be redefined, especially with respect to Clinical R&D. Pharmaceutical Development must, however, create alliances with a host of groups: (1) Discovery - defining lead and back-up compounds; (2) Project Management - making Pharmacy issues an integral part of the project planning process; (3) Clinical - managing supply needs for immediate and later trials; (4) Manufacturing - achieving a seamless technical transfer to commercial manufacturing; (5) Regulatory Affairs - managing multiple regulatory filings

for worldwide regulatory agencies; and (6) Marketing - managing product-line extensions (PLEs) before initial marketing applications are submitted.

1. Alliances with Discovery:

Proactive Strategic Development can create links between Pharmaceutical Development and Discovery and ensure that the organization chooses the right compound/salt form while exploiting the unique biological and physicochemical properties of the chosen drug molecule. Drug Delivery can help Pharmaceutical Development establish links with Discovery (*i.e.*, absorption, biotransformation, clearance, targeting) and exploit biological properties, but such groups may be either central or peripheral to the Development group. Technologies for targeting "non-specific" products (*e.g.*, anti-sense nucleotides, *etc.*) or developing carriers (*e.g.*, liposomes, *etc.*) may even be external to the corporation. Exploiting the physicochemical proprieties of drug products requires tools as well as expertise to do so (*e.g.*, thermal activity monitors, compaction simulators, *etc.*). The corporation may have to be educated to the risks of failing to provide such financial support to clinical manufacturing groups. Competition through manufacturing[19] is impossible when such groups experience benign neglect by much of the organization.

2. Alliances with Project Management:

Pharmaceutical Development rarely has a significant role in regulating the influx of NCEs assigned to its staff for formulation and manufacture. Project management frequently judges an NCE on the basis of *ad hoc* proposals from Discovery or Marketing groups who may be ill equipped to address the "strategic worth"[19] of a project on the basis of pharmacy issues. An "aggregate project plan" is suggested where NCEs are evaluated in terms of potential products which are developed as derivative, breakthrough, or platform projects which require an early evaluation of formulation, analytical, and clinical manufacturing issues[20]. Clearly, development of either a metered-dose inhaler

(MDI) or a dry-powder inhaler (DPI) by a firm new to the technology is a breakthrough project that requires major investment of time and resources by a Pharmaceutical Development group.

Industrial Pharmaceutical Scientists must increasingly manage products which are in-licensed, sometimes with little warning. Rarely does the organization assure sufficient technology transfer during contractual agreements. Frequently, Pharmaceutical Development has no established role in the contract negotiation process and must assume that little to no formulation work has been done. Alternatively, Pharmaceutical Development often has no established role in out-licensing. The organization may also have little understanding of the risks of out-licensing too soon (*e.g.*, serendipitous findings in clinical trials) or too late (*e.g.*, resource drain, particularly on Pharmaceutical Development).

3. Alliances with Clinical R&D:

Managing early clinical trial supply requirements is largely driven by strong corporate pressure to get clinical studies started. Development must balance safety and stability issues for first trial supplies against the longer term focus of creating a commercial product. As many compounds fail to progress beyond Phase I and early Phase IIa trials, Pharmaceutical Development must efficiently accommodate the requirements of the dosage form type as well as the unique physicochemical nature of the compound of interest. An efficient Phase I strategy is critical: keep it simple.

Prospective planning for Phase IIa trial needs can be commensurate with Phase I trials and yet directed towards the commercial composition. A strategy for managing analytical testing for Phase I and IIa clinical trials must include local regulatory requirements for excipient certification as well as unique testing requirements for specific dosage form types. The development of the commercial composition depends largely on the implications of changes in the

synthesis of drug substance, including both route of synthesis and scale-up of drug substance manufacture. Strategic planning of bioequivalency studies parallels process development. Bioequivalency data may have critical launch implications as well, especially when "mill and fill philosophies" prevail. Management of comparator trials can be a Development nightmare when Phase III clinical trials are multi-country studies, when sourcing is difficult, and when export problems exist. Unfortunately, PMA corporations no longer seem to collaborate in such gentleman's agreements that once provided for exchange of comparator formulations as needed in the spirit of reciprocal altruism for the efficient advancement of new therapeutic agents. Interestingly, Japan legislates such exchanges of comparator formulations therein.

4. Alliances with Commercial Manufacturing:

Transfer of manufacturing to commercial plants typically occurs just prior to launch of a newly-approved commercial product. Processing and testing information is often passed *in toto* and just-in-time. Technology transfer can actually occur throughout development, creating a process focus in addition to a product focus[21]. The participation of commercial manufacturing in such continuous information exchanges with R&D clinical manufacturing is especially critical for biologicals that have unique scale-up, analysis, and regulatory constraints[22]. Excipient choice, sourcing, and compendial certification and even equipment[23] issues should be addressed early so that Pharmaceutical Development can minimize scale-up problems and inequivalent commercial batches. The payback to the organization of such internal business exchanges would surely be high.

5. Alliances with Regulatory Affairs:

Regulatory Agencies worldwide are redefining the rules for the review and approval of both clinical trial applications (CTAs) and marketing authorization applications (MAAs). A single example of such changes in

Agency thought is the FDA's recently expressed preference for dissolution profiles rather than single point dissolution specifications for tablet formulations[24]. CTAs and MAAs themselves are also necessarily more complex for many newer products (*e.g.*, peptides, biologicals, *etc.*). Agencies are reviewing more critically the environmental impact of clinical as well as of commercial manufacture, especially for biological products. Pre-approval inspection of referenced manufacturing sites has become the norm prior to MAA approval. Like it or not, corporations have an image at the FDA and other regulatory bodies (*i.e.*, minimalist, contemporary, *etc.*) which should never be ignored. Additionally, the minimum FDA standard in 1992 may not be good enough in the year 2000. Strategic plans written today must assume a tougher regulatory climate in the next century. Being able to successfully anticipate shifts in regulatory trends is a prescription for success in developing products when the cycle time can be as long as 5 to 10 years.

Pharmaceutical Development has a certain ownership of the regulatory claims being made about the manufacture of the clinical drug product. The ownership may be assumed only when Agency questions are received by Regulatory Affairs departments. Pharmaceutical Development's management of regulatory claims depends upon control over any regulatory reports describing the drug product which are forwarded to the Agency. Can Pharmaceutical Development be assured that the Regulatory Affairs section of the organization has sufficient technical expertise to handle the information forwarded to it? Pharmaceutical Development must have reasonable control over technical decisions on filings describing the drug product. The temporary Regulatory subsection of the AAPS which was recently formed suggests a proactive measure to address the need for stronger ties between Pharmaceutical Development and Regulatory Affairs departments.

6. Alliances with Marketing:

The potential benefits of strategic alliances between Pharmaceutical Development and Marketing groups are rarely considered. The payback to the

corporation for a continuous interchange with Marketing can be quite large, especially for product line extensions (PLEs). "Major" PLEs are typically driven by Pharmaceutical Development and include second generation products with enhanced safety, delivery, or stability. Clearly, such products can extend the commercial potential of corporate franchises. Major PLEs can even be formulated before launch of the initial commercial image and then be strategically introduced into the market to counter anticipated competition.

"Minor" PLEs are typically driven by Marketing and include second generation products that differ in color, taste, or tablet shape. Though such products are of lesser scientific interest, efficient development of such formulations provides a significant financial return to the corporation. Pharmaceutical Development needs to support such work while minimizing the impact on the timely development of NCEs.

BENCHMARKING

Even after Pharmaceutical Development has established equal partnerships with critical groups within the organization, an analysis of the performance of Pharmaceutical Development groups within other corporations is necessary. Benchmarking with the best[25] is one way to evaluate performance compared to groups in other organizations with respect to both efficiency and quality. Obtaining such data is difficult. Objective assessments may be performed by peer review confidentially administered by non-aligned review boards including academicians or retired industrialists. Perhaps, PMA-sponsored benchmarking is essential to characterizing the current status of Industrial Pharmaceutical Sciences. Surely, a realistic assessment of Industrial Pharmaceutical Sciences is essential to define the future directions of the discipline.

Benchmarking can address both efficiency and quality, but the measurement of these parameters is compounded. Efficiency can mean elapsed

time for formulation development/employee, elapsed time for analytical development/employee, stability cost/project, temporary staffing costs, contract/internal work ratios, cost of development/employee, *etc.* Alternatively, quality can be inferred from data on the number of recalls/employee, the number of patents/employee, the number of publications/employee, the number of CTAs or MAAs/employee, the technical complexity of formulations or analyses, staffing ratios, professional profiles, *etc.*

Effective benchmarking includes comparisons with current and anticipated future operations of an organization and its competitors. The value of such knowledge is highly dependent upon an organization's ability to effectively respond to it. Though "quality is free"[26], it is not necessarily easy. Even a trained, committed staff requires the support of upper management and the organization as a whole. Though continuous improvement efforts may be driven by Pharmaceutical Development, they need buy-in from the the rest of R&D, Commercial Manufacturing, Marketing, and especially senior corporate management.

TOTAL QUALITY MANAGEMENT

Benchmarking efforts must be rolled into departmental initiatives toward total quality management (TQM). Such efforts are long-term and require support from members of Pharmaceutical Development groups at all levels, especially from the top. Managers of Pharmaceutical Development groups must not only believe in the group's mission they must also live it and reward it[16]. Individual quality initiatives across formulation, analytical, QA, clinical manufacturing, and support staff groups must be fostered and substantively supported by managers. Incremental projects that propose continuous improvements provide return not only to Pharmaceutical Development, they also help create a learning organization where formulators, analysts, clinical manufacturers and other staff members cross-train one another. Incremental projects require minimal capital[8], but management support will necessarily

include training in TQM and statistical tools. Though grass roots efforts can be applauded, "amateurs teach amateurs how to be amateurs"[26]. For TQM to work, management must provide expert support when necessary.

A results-driven continuous improvement program will include cycle time reduction efforts if timeliness is part of a group's mission. Pharmaceutical Development will work with Human Resources to modify personnel evaluations to make individuals at all levels accountable for performance on action teams and reward them when appropriate. Innovation and efforts towards continuous improvement should be given special focus and special reward. Rewards are not always financial, but may be community or management recognition for a job well done[16]. A well designed continuous improvement program is driven by the ranks and empowered by management. With time, such efforts can be directed outwards to the rest of the organization to optimize strategic alliances within the organization. Ultimately, TQM programs can even include suppliers[27].

CONCLUSIONS

Only after improving both internal and external business exchanges can groups of Industrial Pharmaceutical Scientists develop the discipline and enhance the competitive edge of a given parent pharmaceutical corporation. Competing on capabilities[2] cannot be avoided and must include short-to-medium term tactics that fully utilize the staff, facilities, and technologies available. Competitive innovation[7] is also necessary; a substantive strategic intent for a Pharmaceutical Development group must extend beyond current resources, technology, and knowledge. Successful strategies for Pharmaceutical Development must include the ability to anticipate the future of the marketplace, the Agency, the discipline, manufacturing technology, and even the organization.

Pharmaceutical Development staff must be generally cross-trained to be able to intelligently manage the diverse discipline known as Industrial

Pharmaceutical Sciences. The Pharmaceutical Development organization must become a well integrated dynamic learning organization that can drive inter-departmental alliances and teach the rest of R&D not only what the discipline does but how we all must "learn to dance"[5] in an ever changing global industry. Only following internal and external evaluations of Pharmaceutical Development's role and performance, can Industrial Pharmaceutical Scientists strategically advance towards the twenty first century with a discipline intact and strong and able to meet the business and scientific challenges of the pharmaceutical industry of the future.

REFERENCES

1. AAPS Task Force, Pharm. Res., 7, 782 (1990).
2. G. Stalk, P. Evans, and L. E. Shulman, Harvard Bus. Rev., March - April, 57, (1992).
3. Scrip, 1723, 12 (1992).
4. N. S. Langowitz and J. B. Graves, Res. Tech. Manag., March - April, 39, (1992).
5. J. A. Belasco, "Teaching the Elephant to Dance," Crown, New York, 1990.
6. R. H. Schaffer and H. A. Thompson, Harvard Bus. Rev., January - February, 80, (1992).
7. G. Hamel and K. Prahalad, Harvard Bus. Rev., May - June, 63, (1989).
8. R. H. Hayes, Harvard Bus. Rev., November - December, 111 (1985).
9. K. Mansford, Scrip Magazine, March, 28, (1992).
10. R. M. Birch and D. J. Kyle, Pharm. Res., 8, 141 (1991).
11. K. R. Freter, Pharm. Res., 5, 397 (1988).
12. T. M. Brodsky, Pharm. Res., 5, 1 (1988).
13. W. Szkrybalo, Pharm. Res., 4, 361 (1987).
14. E. Broshy, Pharm. Exec., May, 70, (1991).
15. R. S. Kaplan and D. P. Norton, Harvard Bus. Rev., March - April, 71 (1992).
16. T. Peters and R. H. Waterman, Jr., "In Search of Excellence", Harper Collins, New York (1982).

17. J. R. Ignizio, in "Artificial Intelligence Applications in Chemistry," T. H. Pierce and B. A. Hohne, eds., McGraw-Hill, New York, 1991, p. 37.
18. N. J. Grange and A. W. Pearson, R&D Manag., 19, 27 (1989).
19. S. C. Wheelwright and R. H. Hayes, Harvard Bus. Rev., January - February, 99 (1985).
20. S. C. Wheelwright and K. B. Clark, Harvard Bus. Rev., March - April, 70 (1992).
21. R. H. Hayes and R. W. Schmenner, Harvard Bus. Rev., January - February, 105 (1976).
22. M. D. Giddins, R. Dubbah, L. T. Grady, and C. T. Rhodes, Drug Dev. Ind. Pharm., 13, 873 (1987).
23. T. M. Pack and E. A. Cunfer, Drug Dev. Indust. Pharm., 14, 2687 (1988).
24. C. Kumkumian, "The Pink Sheet"®, F-D-C Reports, Inc., 54 (18), T&G-15 (1992).
25. T. G. Tucker, S. M. Zaran, and R. C. Camp, Harvard Bus. Rev., January - February, 8 (1987).
26. P. Crosby, "Completeness: Managing in the 21st Century", Satellite Conference on Quality Management, 28 April (1992).
27. M. Barrier, Nation's Business, May, 22 (1992).