Table 5. Number of patent applications field in India

Year	Indian	Indian (percentage of foreign)	Foreign	Total
1986–87	983	39.2	2506	3489
1987–88	930	36.8	2527	3457
1988–89	1077	42.8	2516	3593
1989–90	1039	39.6	2621	3660
1990–91	1180	45.7	2583	3763
1991–92	1293	57.2	2259	3552
1992–93	1228	54.8	2239	3467
1993–94	1266	48.6	2603	3869
1994–95	1741	48.5	3589	5330
1995–96	1606	29.5	5430	7036
1996–97	1661	24.0	6901	8562
1997–98	1926	23.3	8229	10155

1339 such applications were received[3]. Although there is no published data as to how many of these applicants have sought EMR, it is believed that the number is very small to draw any objective conclusion at this stage to directly correlate the post-WTO patenting in USA to the amendments in the Indian Act.

Future perspectives

The emerging global presence of India in the field of technology in the post-WTO phase is just one small step. There is a long way to go for the country to strengthen its technological base and carve out a niche in the international technology trade and market. For this purpose, it is important that the R&D organizations in the public and private sectors join hands to develop a portfolio of patents on narrower fields of critical technologies based on their core competencies. Patent analysis can help in finding out such niche areas.

We have obvious strengths in terms of lower costs of research, high quality of scientific competence and flexibility to respond to these new global changes. We need to keep pace with the changes taking place in the global R&D scenario and evolve appropriate responses to them. The external orientation of R&D institutes in India would need to be balanced by an appropriate thrust towards the requirements of the Indian industry and business. While some of the Indian companies are taking steps to re-engineer their structures, a vast majority has to learn to use knowledge to create wealth and transform their business to be driven by research and development.

1. The Patents (Amendment) Ordinance, 1999, Government of India, *The Gazette of India*, 8 January 1999, New Delhi.
2. Annual Report, Controller General of Patents, Design and Trade Marks, 1997–98, Government of India.
3. Gangly, P., *Chem. Ind. News*, April 1999, **XLIV**.

Received 6 December 1999; revised accepted 1 February 2000

Gentle drugs: A new paradigm for drug development

V. Sitaramam

Searching for new drugs is guided by their specificity and potency. The methodology, including the statistical approaches, orients itself to do exactly that. More potent drugs also have more side effects, a technology trap that requires a radical re-examination regarding how to go about drug discovery. It is relevant in an era when quality of life is emerging as more important than the ill-kept promise of dramatic therapies. Interestingly, the problem statement can be formalized and a strategy can be identified that requires new methodological grounds to be covered within the scope of allopathy.

AN analysis of the current information and trends, commercial and scientific, regarding the status of drug development indicates an outline of an unfilled niche in drug development of interest to the pharmaceutical and related industries. The high cost of drug development is remediable by a major effort in rethinking on its science. What is more interesting is that this very rethinking would involve matters that would lead to a new emphasis in drug development. One such direction may be

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termed the 'Gentle Drugs'. This particular niche has never been adequately filled nor even addressed to and would probably represent a market size *in between* that of the current pharmaceutical industry and that of life style industries including various stimulants, beverages and even food.

What is a 'gentle drug'? A 'gentle drug' is not simply a drug with 'gentle' action, i.e. without side effects, etc. It is not necessarily a natural product. It is the obverse of a good drug. What is a good drug? One that is specific, one that is potent and one that is without side effects. What is a side effect? There are two kinds of side effects. If you have a drug that kills only T-cells, and nothing else, the drug may not have other effects. But killing of T-cells will have! On the other hand, a drug that kills 60% T-cells and 40% the intestinal mucosa will indeed have side effects as we commonly understand. But *both* are side effects. Therefore, all drugs which are good will be potent and will have side effects... sooner or later. On the other hand, a gentle drug is relatively specific *but modest in its action* in the acceptable therapeutic range. There are no examples of gentle drugs to date because they represent a class of drugs which are normally rejected in the protocols of discovery. Cyclosporin may be the only example that comes to one's mind (note 1). Gentle drugs represent a class of drugs which cannot be conceived by the current methods of drug screening and get junked. It is this methodology that creates an operational class of 'gentle drugs' and not as natural products or synthetic chemicals.

Pharmacoeconomics: what makes drugs expensive?

Drugs are expensive. That is why they are lucrative. Drugs control diseases. That is why they are needed. Such drugs are needed in small quantities and require active supervision. Being specific, their potency is varied and the chance of finding the next antibiotic and the next vitamin decreases exponentially. Need for drug development arises for two reasons: side effects in general pharmacology and resistance in antibiotic therapy. Effective drugs decrease the market, while increasing the profits. Money for drug development comes from profits of previous drugs. Thus it is always limiting in drug development. The market primarily decides the overall throughput of expenditure on drug development. If it costs about US$ 230 million and a decade for an organic chemical aspiring to be a drug and US$ 120 million for a biopharmaceutical agent, the costs can be staged and the defrayable cost can be worked out as shown in Table 1.

Thus, based on probability of stage conversion in trials, each drug costs more as the *trials are inconclusive* till the costs are prohibitive. There is an insurmountable problem as well as an extraordinary opportunity here. What is the contribution of the borderline drug which gives inconclusive results to the over-all costs?

The quest for the P value

It is logical that our methods of enquiry are often determined by the mind sets we have. Let us consider the case of finding a new drug. The probability of this event, the probability of finding the right level of activity, would be small. We can rightly say that the probability of finding a drug exponentially decreases with its potency. Let us consider a realistic situation where the sample size is large and yet the effect of a finite magnitude compared to a god-fearing placebo would just about carry a probability of 0.05. More or less. The drugs that are much less effective than this are weeded away early in the game. The drugs which are more effective are picked up. The toxicology will weed out a few and the 'right' drugs, however rare, will emerge. Thus we can speak of a situation wherein the possibility of staying on a drug trial exponentially vanishes as shown in Figure 1 on either side of this 0.05 level significant effect. Those at $P = 0.05$ are like Buridan's ass and can neither be rejected nor be accepted. The effect is low and so is the toxicity. The indecision associated

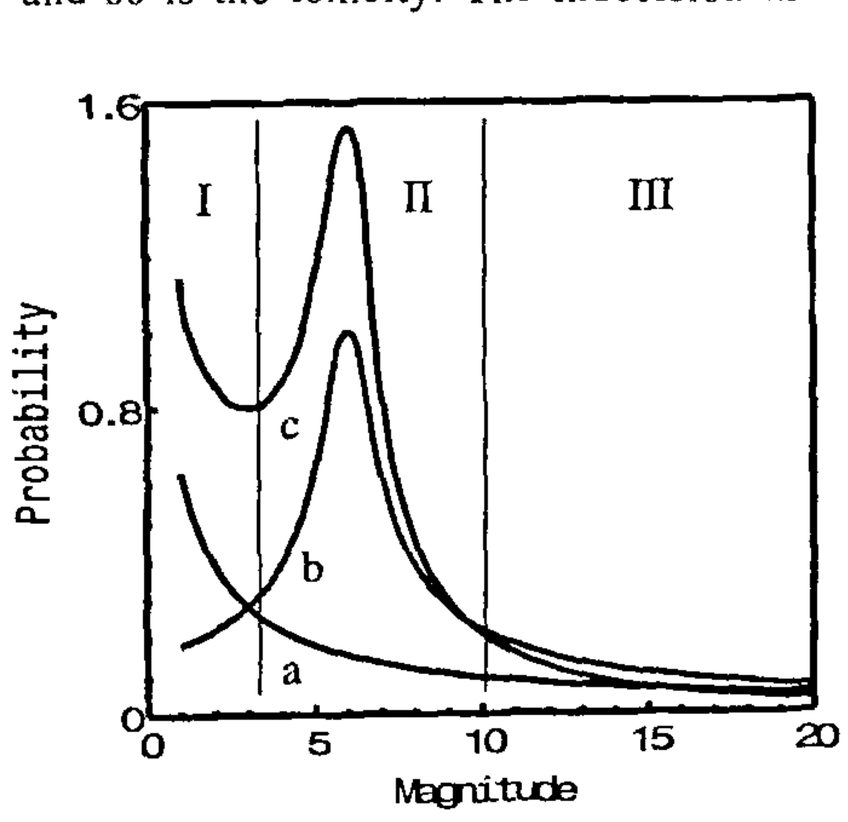

Figure 1. Zones of economics of drug discovery. The figure depicts three zones of economics of drug discovery. Eschewing the formalisms and simply stated, the % probability of finding a drug of a given magnitude of effect is as with curve a. There exists a magnitude which is indeterminate for the maximal sample size of patients available for testing, say the value 6. The % probability of its being retained without a decision decreases exponentially on either side as seen in curve b. The product a.b as seen in curve c depicts a multimodal curve that defines three domains differently shaded: domain I wherein the cost contribution is high because there are so many compounds which are useless and domain III which has highly effective drugs retained and highly toxic drugs which are discarded early so that costs are low and returns are high. *The intermediate domain II is the domain of indecision due to nature of the magnitude and statistical indeterminacy leading to no returns and high costs. This is the domain of gentle drugs.*

Table 1. Costing of drug development in case of biopharmaceutical companies

Stage	Cost (million US$)	Time (years)	Cumulative time (years)	Transition probability	Drug throughput	Cost throughput	Defrayable cost	% Defrayable cost
Preclinical	20	2.3	9.9	0.537	1	20	198	47
Phase I	25	1.8	7.6	0.873	0.537	13.43	102	24
Phase II	25	2.2	5.8	0.833	0.469	11.7	68	16
Phase III	25	2	3.6	0.923	0.39	9.76	35	8
Regulation/launch	0	1.6	1.6	1	0.36	0	0	0
Total	95–125					Total	403	

Cost includes the bank interest that is to be paid over time, which cannot be done till the drug earns money.
Viable sales = α defrayable cost
where α = financial factor (interest, inflation, market goals, etc.)
Time for each stage = t_s
Cumulative time from stage 's' onwards = $\sum_{j \geq s} t_j$

Cost at each stage = C_s
Transitional probability for each stage = P_s
(probability of entering stage 's' given, system in stage 's-1')

p (reaching stage s) = $\prod_{j=1}^{s} p_j = P$ (Drug throughput to stages)

Cost throughput = $C_s\left[\prod_{j=1}^{s} p_j\right]$: C_s = specific cost for stage 's'

Defrayable cost at stage 's' = $C_s \left[\prod_{j=1}^{s} p_j\right]\left[\sum_{j \geq s} t_j\right]$

Total cost = $\sum_{s} C_s\left[\prod_{j=1}^{s} p_j\right]\left[\sum_{j \geq s} t_j\right]$ and hence % for each stage.

with it will progressively increase the clinical and other testing load (see above) and therefore will add to costing of clinical trials demanding larger and larger and therefore more expensive trials. Thus the product of these two probabilities will give us a probability of it being expensive as a class to drug testing that is solely based on a level of significance, regardless of the level of significance. We readily see that there being far too many drugs at the lower end of the spectrum of activity will also confer high costs simply because there are so many of them. On the other hand, highly active compounds will not cost so much since they will either be toxic and therefore weeded out or will be acceptable and therefore will be rewarding as new drugs.

There are a series of decisions on potency and toxicity for a single drug, all of which contribute to indecision each with its own P value. Thus the window of indecision becomes broader as also the duration of the trials. This is why while a single trial lasts 4–6 months, clinical trials on an average take over 2 years.

Conversely speaking, the drugs that contribute to costs are one assured source of the *gentle drugs*. They are being weeded out on a potentially wrong premise. The dose response curve of a drug could be low and linear with early saturation in effect or it can be acutely sharp and saturate readily. The latter will show a great deal of significance even in the face of large inter-individual and intra-individual variations. The lower drugs will often give ambiguous results, particularly in the field. But in a given situation of low level fine tuned control of, say marginal diabetes wherein the patient responds to any anti-diabetic violently even at small doses, it is the low long term control that gives the edge in protection.

Testing for gentle drugs

There are three premises to consider. Firstly, statistical significance is necessary and not a sufficient condition. The magnitude matters. Magnitude assessed independent of sample size would be a true test of response, either in a controlled experimental situation (as with increasing reliance on *in vitro* testing would argue for) or in a single individual with multiple testing, if feasible. Secondly, when samples become large enough and when they significantly differ in some attribute not merely in their mean values but in their distributions, testing becomes unreliable. Thirdly, since each drug carries some

risk, it needs to be shown somehow (note 2) that the effect of the drug does not become less than risks incurred to be accepted on one hand; also, the low risk associated with a drug does not merely lead to its rejection against a more effective and yet much riskier drug. Gentle drugs, their sourcing, as well as testing for efficiency, risk, quality of life they offer and overall value all require new statistical strategies.

Gentle drugs as a real alternative

What do we mean by a gentle drug? Let us compare them with the standard drugs, SD. Table 2 provides the operational 'definition' of the gentle drug. We would like to present the gentle drug as an *alternative* market niche to herbals on one hand and SD on the other.

The accent in SD is specificity. Molecular basis is the altar at which even patient comfort can be sacrificed with impunity. Mechanism is the buzz word. Scientific credibility is the creed. Proof and confirmation themselves should be based on robust methodologies proven for decades. '*P*' shall be much less than 0.05! SD cuts through disease with the blade of potency. High potency runs the risk of high toxicity and high toxicity means higher levels of suffering but then that is the price to pay for specificity and potency. There are exceptions but they prove the rule.

So if we need GD, the accent is on low toxicity and low suffering. This matters over and above everything. But then, we may sacrifice some potency. But we *cannot sacrifice the evidence, i.e. the need to show that the drug acts.* Since we recognize the need to carefully look in the other direction (low potency), we would need to look at the problems of low potency drugs. The major threat here is the technology trap (note 3). We need to first examine the subtle difference, the thin divide, between 'low potency' and 'no potency'. 'No potency' are the herbals.

The catch is that no such a thing like a drug without toxicity. Its direct corollary is that there is also no true placebo! Drugs and sugar pills are a consequence of looking at molecules, forgetting men on whom they act!

GD need not be confused with one unfortunate popular bias. These are not herbals in the populist sense. Pure placebos are one thing. These are products of hard science. Herbals are another. These are anecdotal, apocryphal and cultish. Their appeal as drugs lies in unconventionality, appeal of incoherence and even anti-conventionalism. Folk remedies, alternative forms of medicine, natural products... there are many ways in which the herbals make their appeal. Are herbals placebos? The strongest lesson comes from tea, coffee and tobacco. All the three are classic herbals. So is cocoa. Herbals loom largely on life styles. Which is a mere herbal?!

What does the gentle drug offer the consumer?

Unlike many herbals and panacea, the gentle drug does *not* offer the consumer excessive hope or promise. The gentle drug *does*, however, offer an *informed choice.* It manages. Globally there is a growing discontent (and disenchantment) with the practice of medicine that vests all decision making in the hands of the medical authority. Clearly many consumers of medical services do not wish to lose control of what is done to their bodies. They would like to have information, alternatives, risks and benefits articulated clearly. But they would like to make a personal *choice*. Large numbers of intelligent and otherwise rational individuals drift towards spurious 'alternative therapies' which range from the innocuous like homeopathy, flower-remedies and aromatherapy to those which are potentially dangerous. For most of these individuals, the switch to these therapies is a 'negative' choice; because conventional allopathic medicine does not allow them to participate in the decision-making process, nor does it offer alternatives. The largest fear that practitioners of alternative therapies play upon is loosely called 'side effects'. Gentle drugs allow the patient the choice of balancing potency vs toxicity (the 'side effects'). Another factor in favour of 'alternative therapies', particularly in the developing countries is their substantially lower cost. Gentle drugs can offer the consumer the option of balancing potency vs. cost. In a large range of disease conditions that are not life-threatening, there is considerable scope for the patient to exert a choice in the therapy. These include: duration of therapy, degree of discomfort he/she is willing to bear, short-term vs long-term health benefits, route of administration, cost of the therapy, etc. Similarly, in the case of chronic or terminal illnesses, the therapy is only palliative and not curative. Nevertheless, these therapies often cause intense discomfort/pain, or steal the dignity of the patient. Here again gentle drugs could offer a range of options from which the patient, the physician, and the patients' family can evolve a strategy that best suits the particular individual.

Limits to statistics

The plaintive cry of the trial manager seeking us to 'beware of statistics' is common knowledge. For the falling person, warnings are too late. Support is what is needed, which is the case with the high cost of drug development. The major problem is not the applicability but the limitations of statistics. Statistics is best used for large effects handling small numbers and when the science is clear and predictable. Everywhere else, it fails rather than it delivers. Since the decisions rest on magnitudes and not on significance, and since significance is often entirely dependent on numbers one plays with, the

statistician has little advice to offer than to increase the numbers. In this sense the in-house statistician and the consultant statistician differ since the former alone is accountable within the organization for the money his suggestions would cost to the organization. The actual problem is that the cut-offs where a drug is to be abandoned or pursued are to be determined by the costing. All conventional methodology for standard drugs ensures that gentle drugs are missed, hence the need for an operational strategy rather than the worship of the null hypothesis (note 4).

Risk analysis

Duration of therapy, degree of discomfort a patient is willing to bear, short-term vs long-term health benefits, route of administration, cost of the therapy, etc. can and should be matters of choice. Gentle drugs are about making choices in an environment where black and white models are inappropriate. They explicitly address the grey area where individuals (both physicians and their patients) must constantly balance the costs with the benefits. Such a choice can only be meaningfully exerted when the risks involved can be quantified in a manner that allows a comparison between the risks posed by alternative strategies. This emerging area in statistics is of central concern to insurers, stock-market operators and all those whose products pose a significant risk to users, i.e. from Styrofoam cup makers to automobile and cigarette giants. The effective marketing and widespread use of gentle drugs can only come with the parallel development of credible 'risk maps' that place the benefits and costs of a range of drugs of varying levels of potency and toxicity on a common map and compare these with the risks imposed by life-styles such as drinking tea or coffee, smoking or eating French-fries. These must be compared with the cost (or risk) that the particular disease itself puts the patient.

Quality of life

There is a growing disenchantment with the inability of Western medicine to find cures for the diseases of the aged, the chronic and long-drawn disease conditions like cystic fibrosis (a classic case where one does not know what to do with the gene after much jubilation on identification!) and painful diseases like cancer. Quality of life is what increasing number of such patients are demanding and many hospitals, religious groups and even courts are sensitive to. But quality of life is notoriously difficult to judge. However some universal measures are evolving. For example, a commonly-used parameter is the QUALY (Quality Adjusted Life Years) which is basically a quantification of the question 'how many years of your life in your current state of health would you trade for one year of perfect health?'. The hostility of patients is essentially addressed to a system that forces them to endure a poor quality of life and vests the decision in a medical authority. If gentle drugs are to make inroads in this segment, they must adopt innovative statistical measures (without eschewing credibility) to demonstrate that they are 'patient friendly'.

Demonstrating value

One of the fastest growing disciplines in recent years has been pharmacoeconomics, the study of health-care costs and outcomes. This is the direct consequence of the market demand on the drug industry to demonstrate value. These studies have become popular because they have successfully allowed the introduction of some astronomically-priced products by changing the image of the drug from *costly* to *cost effective*. Regulatory agencies, health insurance companies and Managed Care all find pharmacoeconomic studies indispensible. Thus, it is possible (and acceptable) to quantify many intangibles like travel to and from hospital, productivity losses through absence from work, costs of medical personnel and equipment which are necessary for the treatment, etc. For gentle drugs that are less demanding on facilities and medical supervision, pharmacoeconomics would provide a powerful marketing tool.

I have outlined in Table 1 a typical case of costs in drug development based on drug throughput and the formalisms associated with these calculations. The only difference in the calculations as opposed to the usually seen versions is that a clear distinction is made between incurred cost and defrayable cost. The latter stems from the fact that bank loans have to be repaid. The conclusion is opposed to what the drug companies would have us believe. Drug discovery is even more expensive as a defrayable cost.

Table 2. Comparison among SD, GD and herbals

Standard drugs	*Gentle drugs*	*Herbals*
High activity	Low activity	Little activity
High toxicity	Low toxicity	No toxicity
Specific mechanisms/ targets	Modulators	Placebos
Curative	Supportive	Supportive/ Psychophysical
Scientific	Doubtful*	Cultural/anecdotal
Rarely felt need	Often felt need	Common need
Via professional pharmacists	OTC	No restrictions
High cost of development	Very high costs**	Very low

*By the current methodologies.
**Reducible to manageable levels given right inputs in information technology, policies for sharing high risk sharing discoveries and better statistical methodologies. OTC, over the table.

Managing information

Information and its management is central and critical to the concept of the gentle drug. Development of gentle drugs demands a revamping of the concept of the R&D centre. The premise is that the borderline rejects of pharmaceutical research over the last fifty years are rich picking fields for potential products. Ironically, the sheer size of this basket could become its most serious disadvantage. Managing this knowledge and information glut (which will be prohibitively expensive without some conceptualization for information retrieval) thus becomes the key task of the R&D centre. This will undoubtedly require the development of novel and powerful information technology usage protocols to utilize the available information to the full advantage and cost-effectively. These technologies must streamline procedures to procure, purchase, generate, manage, analyse and report information. More importantly, they must develop capabilities to *put a value* on available knowledge, both within the company and that of other companies. It must be able to 'trade' based on these valuations buying knowledge, adding value to this knowledge and selling it. It must have the capacity to evaluate for effective purchases of knowledge and barters or strategic alliances to maximize return on resource allocation. When the number of choices *vis-à-vis* potential products are very large, the management of the risks involved in making choices itself becomes critical. In the increasingly complex environment in which companies will find themselves, successful choices cannot be based solely on the merits of the product's efficacy. The *management of the choices* always relates to all complex questions to which there are no clear yes and no answers... be it the science, be it the disease of interest, or be it the value of the knowledge available for sale, or the allocation of resources, or the terms of trade of knowledge or information... whatever. All these impose risks, which cannot be eliminated but can be contained. But they require serious and sustained investments in new techniques at the frontiers of both information technology and statistics. Above all, these do not reflect science, but the limits of science.

Where gentle drugs are prohibited

Clearly one area in which the notion of gentle drugs is dangerous is the area of infectious disease, primarily because it is transmittable and resistance cannot be encouraged. Thus, this area will remain outside the purview of gentle drugs in the sense that potency has both short-term and long-term payoffs. However, the idea of gentle drugs can be modified here basically to enhance the efficacy/potency against the antibiotics in a very special way and this serves the strategy as well if not even better. We call these the VAG technologies, whic refers to Value Added Generics technologies. The ide is based in targeting the antibiotic better to the interic of the bacterium, thereby lowering the requir ments/enhancing the potency of the antibiotic, makin the combinations re-patentable. This idea, now *fait a compli* and termed VAG technologies (note 5), will b elaborated subsequently.

What market-segment does the gentle drug address?

Consider Figure 2, which compares global consumptio (in billions of US$) in the health-care sector; life-styl activities (such as eating out, beverages and cigarettes medical drugs and herbals. *Drugs have traditionall contributed to less than 10% of health care costs.* It i also clear from Figure 2 that the consumption of drugs i but a small fraction of that of the life-style sector. W envisage the gentle drugs while occupying a specifi niche, also as servicing a grey area that spans all thes sectors. A gentle drug could be, at its lowest, a certifie placebo used in a hospital environment and serving medical need; a low potency drug to manage toxicity offer symptomatic relief in a chronic condition; be comfort medicine for the aged; or even a low-potenc drug with dosage individually fine-tuned under intensiv management for specific conditions like marginal diabe tes. It does not replace a specific remedy. It cannot b brought into market without the best that informatio technology can offer since marginally effective drug

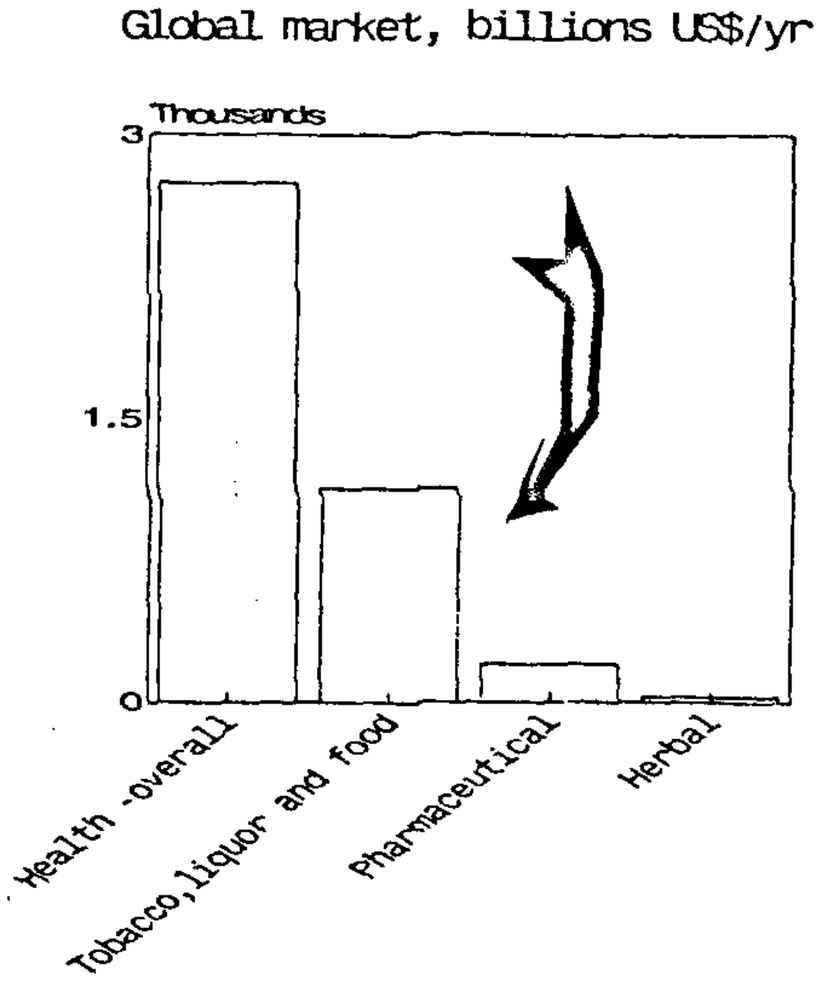

Figure 2. Global market of health and life style commodities. The black arrow indicates the unfilled niche of gentle drugs.

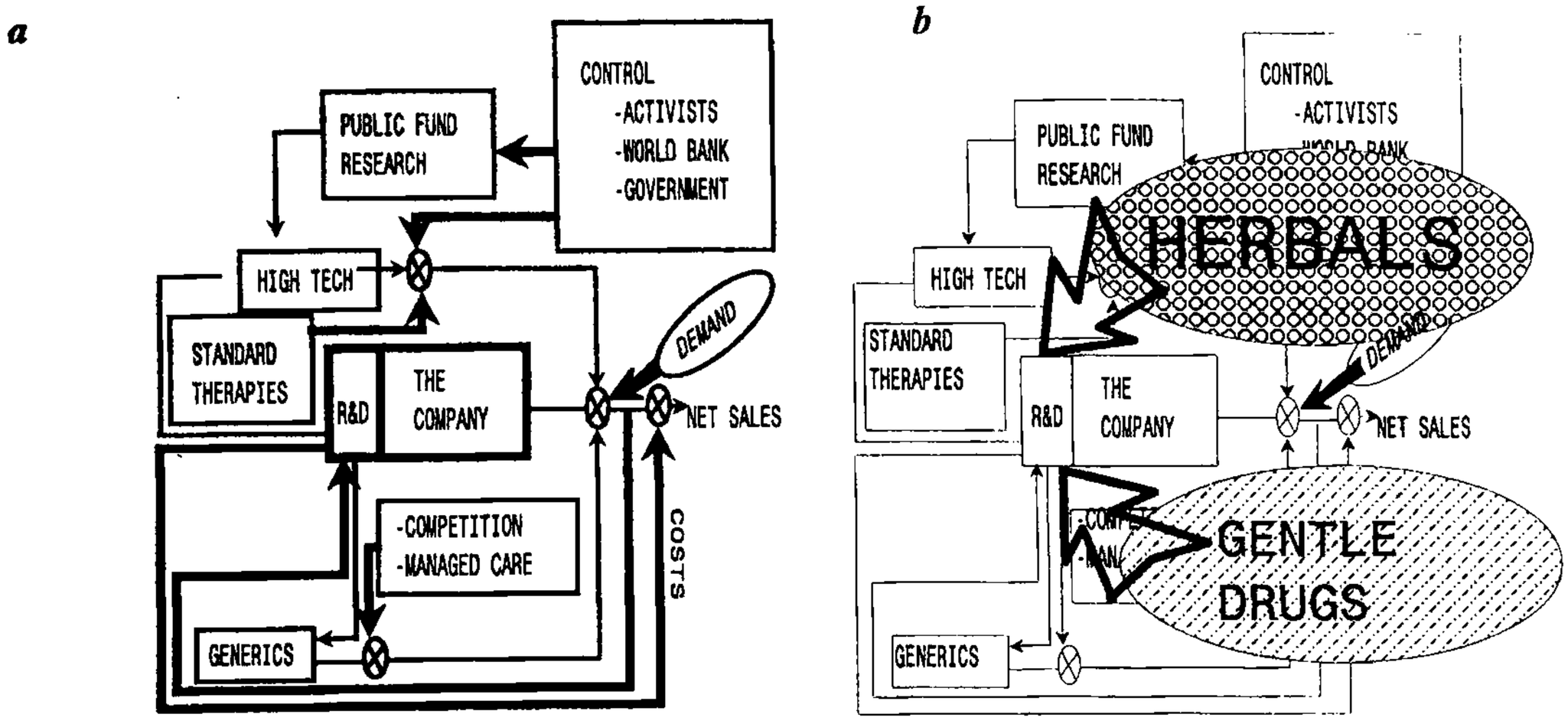

Figure 3. The interactions in drug industry. *a*, The dark lines are negative interactions. The thin lines are positive inputs. Demand function, which is clearly positive, is kept outside these interactions since it is the dominant influence over and above all these interactions. *b*, The interactions in Figure 1 *a* represented in the background, superimposed by herbals and gentle drugs. Clearly, all the ground rules will change when these are superimposed in the higher dimension.

require more than marginal data to sustain and justify their usage.

What does the gentle drug offer the drug company?

We have indicated above that gentle drug is effectively addressing a market niche that is larger than the demand of pharmaceuticals *per se*. Additionally it allows the company an option not to be trapped by the price-wars of the generics on one hand and the outrageous risks that bio-pharmaceutical development entails on the other. Western medicine has gravitated away from the particular and towards the general in the treatment of disease. Thus, it is possible for diverse doctors to prescribe the '*best generic*' for all patients with the same disease condition. The *best* relates almost exclusively to the 'therapeutic window', i.e. highest potency with acceptable (*not minimal*) toxicity, with the accent on potency. The notion that, at least operationally, it is possible to arrive at a therapy that is *best*, is at the core of the success of the Managed Care. It is only when such a notion is implicitly accepted that one can reduce half the population of the United States (117 million) to a single consumer. Gentle drugs, on the other hand, champion the idea that the patient is 'individual' and considerable options can be exerted (note 6). As patients demand to exert these options, the Managed Care will lose much of its bargaining power. Most important, the gentle drugs offer unique ways in which to substantially reduce the overall costs of drug development. These are discussed in detail below.

Drugs and costs: A reappraisal

If one looks at the R&D expenditures and growth of the drug majors and the smaller pharmaceutical and bio-pharmaceutical companies, as particularly relevant to new entrants and developing countries, the need to develop newer analytical/statistical tools and information technologies becomes clear. The focus will be towards cost reduction in drug trials and this is particularly critical in the development of 'gentle drugs'.

These considerations are important if one is (i) a drug major seeking alternative strategies to combat the new threats in the health-care environment, (ii) a small to medium-sized pharmaceutical that needs to manage cutting edge R&D but wishes to contain drug discovery costs, (iii) seeking alternative market segments in health-care. These are also important if one is to cope with the flood of information since the only reliable method to handle information is insight-based. It helps break the tedium of monkey and type-writer strategies in drug development, often far too expensive to handle.

Current market niches and the threats they face globally

In the last few years, analysts in the pharmaceutical industry have come to terms with the fact that the precipi-

tous rate of change, both within the pharmaceutical companies *per se* and in the marketplace, created an environment where the rules of the past (even the recent past) cannot be applied to the future. However, this realization has not translated into a cohesive corporate strategy and the reactions of the pharmaceutical industry to the new threats are still limited by the paradigms of the past. While it is necessary to clearly articulate the dominant threats to the industry, it is equally imperative to recognize the new opportunities, even if these go against the past tenets wherein social acceptability took the back seat.

Figure 3 *a* gives a systems theoretic representation of the forces operational in the pharmaceutical industry. The heavy arrows show the negative forces that are the threats to the industry. These include the Managed Care and other market forces for the generics and soaring drug development costs for the bio-pharmaceuticals. It is clear from Figure 3 *a* that the two-dimensional approach of shifting between generics and high tech biopharmaceuticals adopted by many companies is a vicious circle. Both these sectors are increasingly being faced with threats both from the government and from the marketplace itself, limiting opportunities as well as profitability.

Figure 3 *b* superimposes the 'third dimension' onto Figure 1. These are the herbals and the gentle drugs. Both are largely virgin areas with new and unique opportunities. The opportunities in the domain of gentle drugs are discussed here in this light.

Notes

1. It is anecdotal but the low toxicity is something that spurred the hopes for cyclosporin.
2. That is by designing weights in the assessment of impact.
3. Imagine we are developing combat aircraft. The costs keep soaring with improvements in the design. Ultimately, a single aircraft in future will take care of an entire defence budget, if merely extrapolated. The day will not be far off when development of a single drug will take all the R&D money of the government.
4. Risk analysis is not without risks. Interactive risks, as is common in life situations, have no ready solution for analysis and the strategies would be model-based. Imagine the dilemma of a flying squirrel. When it is on ground it is threatened by the fox. When it is flying, it is threatened by the hawk. Fortunately since the fox does not fly and the hawk does not run into the bushes, the threats are mutually exclusive, hence non-interactive. But if you have hypertension and/or diabetes, what happens to the heart is anybody's guess since all these three make a heady mix and are highly interactive as risks.
5. Sitaramam, V., Indian Patent filed. 1998.
6. Not in the populist sense, but by decisions based on odds computed statistically including parameters that mean something to the patient, e.g. quality of life.

ACKNOWLEDGEMENTS. I thank Dr Zuben E. Sauna for discussions, which led to idea of gentle drugs and Dr Mrs. S. A. Paranjpe who helped with the formalisms. Nearly all the background information relevant is commonplace and can be found in numerous articles that appeared in *Nature Biotechnology*, *Nature*, *Science*, etc. and, being commentaries and data extracts, add little by way of citation and hence their omission.