Pharmaceutical innovation between scientific opportunities and economic constraints

Jürgen Drews and Stefan Ryser

New drugs are only developed when sales expectations appear to match the rising expenditures for development. The repertoire of diseases that are seriously addressed by large pharmaceutical companies is shrinking. Genomics offers the promise of inventing and developing more selective therapies for a large number of diseases, but such increases in selectivity almost inevitably lead to therapeutics aimed at smaller patient populations. Scientific opportunity on the one hand and economic constraints on the other are forcing pharmaceutical R&D in different directions. This study tries to quantify the problem and to identify mechanisms through which the apparent conflict may be resolved.

Modern pharmaceutical research has been shaped by a range of scientific disciplines, including chemistry, pharmacology, microbiology/fermentation and molecular biology. Although the latter discipline has influenced drug research in very broad ways, its manifestations in drug therapy have so far been limited to the use of recombinant proteins and to monoclonal antibodies. However, a broadening of this scope of products is imminent.

With the advent of genomics, the evolution of drug discovery has entered yet another stage: the understanding of gene structure and function will enable assessment of the contributions of genes to disease phenotypes, and this knowledge will open up numerous new opportunities for therapeutic interventions. The drug therapies that are now prescribed address about 500 molecular targets[1,2], including targets that chemotherapy utilizes to kill bacteria, viruses, fungi, parasites and cancer cells. At the molecular level, enzymes form the largest group of such targets, followed by receptors, most of which are G-protein-coupled receptors. Until now, enzymology and 'receptorology' have been the most successful strategies in drug research, but whether or not this situation will remain, given the impact of genomics, is unknown. Many new proteins that are discovered as elements in signalling pathways are indeed enzymes, such as kinases and phosphatases, and enzymes such as acetylases and methylases also play a role in 'closing' DNA sequences for transcription activity. It is clear that the number of drug targets will increase substantially.

If it is assumed that about 100 important diseases burden millions of people in the industrialized societies of the world and that each of these conditions will be caused by 5–10 genetic alterations, we would expect perhaps 1,000 'disease' genes. These genes or their products may indeed turn out to be very poor targets for drug therapy. However, almost all of the proteins coded for by these genes will be parts of signaling pathways and regulatory systems, and if within these pathways each protein corresponds with 5–10 other proteins that are good targets, the number of potential molecular targets for new drugs would increase to 5,000 or 10,000 in a few decades[3].

Jürgen Drews*, Hoffmann-La Roche Inc., 340 Kingsland Street, Nutley, NJ 07110, USA. **Stefan Ryser**, F. Hoffmann-La Roche AG, 4070 Basel, Switzerland. *tel: +1 973 2357635, fax: +1 973 2355008, e-mail: juergen.drews@roche.com

  1359-6446/97/$17.00. PII:S1359-6446(97)01086-6

Genomics, like other innovative technologies affecting drug discovery, will open up many new avenues. Therapies are likely to become more specific: undoubtedly a disease phenotype can be caused by a variety of genetic configurations. From a medical view point it would be highly desirable to deal with different genetic causes for diseases individually. However, the prospect of more specific drug therapies afforded by genetic data runs counter to the economic constraints that govern drug development today.

Between 1976 and 1996 the cost of bringing a new drug to the market has increased tenfold (Figure 1). This increase from $54 million in 1976 to $500 million in 1996 reflects inflation as well as an increase in real dollars[4,5]. Allowing for 4–5% inflation on average, expenditures have approximately quadrupled in the past 20 years. The 1976 and 1996 figures are not directly comparable because they were generated using different methods. However, they all represent the cost of failures as well as the cost of preclinical and basic research required to generate the new drugs. Even if the figures compiled from work by DiMasi[6], Hansen[7], Wiggins[8] and others[9,10] are debatable, the fact that the cost of bringing a new medicine to the market has risen steeply during the last 20 years cannot be contested.

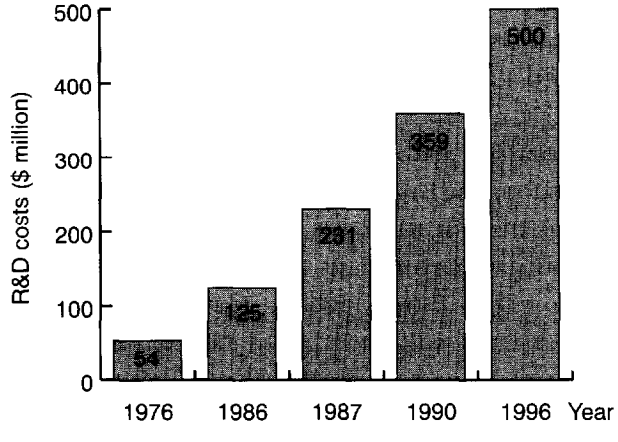

Figure 1. *Costs of bringing a new drug to the market. Using a database from 14 companies, R. Hansen[7] estimated that the average development cost for a new clinical entity tested between 1963 and 1975 was $54 million (expressed in 1976 dollars). He applied an 8% discount rate on direct costs to arrive at the final figure. Using a different method, S.N. Wiggins[8] arrived at an average cost of $125 million for drugs approved between 1970 and 1985. The 1987 figures are based on a Tufts University study of 93 companies in the USA. They applied a discount rate of 9% over a 12-year development time for drugs launched between 1970 and 1986. The figure represents 1987 dollars. The 1990 figure was generated by the Office of Technology Assessment at the request of Senator Henry Waksman. The figure is in 1990 dollars. The $500 million estimate was taken from a paper by H. Schwartz[5]. It was first mentioned in a study by the Boston Consulting Group[9]. All figures represent fully capitalized costs at the end of development.*

In fact, this increase is having very real consequences for development decisions – drugs that satisfy important medical needs but are not meeting the increasingly high financial expectations of a given company are no longer developed. This mechanism may, at some stage, critically narrow the repertoire of diseases and medical problems that are addressed by big pharmaceutical companies. Already, the industry has virtually abandoned large disease domains that represent huge medical needs but are not supported by functioning markets. Examples include tropical diseases, especially malaria, and also opportunistic infections that are closely associated with inferior living conditions, such as tuberculosis. However, the restrictions imposed by a lack of market size or generally by insufficient financial returns go much further; numerous diseases with a worldwide prevalence of one or two million patients fall within the category of doubt. Cancer is a typical example: while a prevalence of more than 19 million cases for all forms of cancer in the developed world represents a formidable market opportunity, many organ-specific cancers occurring at prevalence rates of 500,000 cases or less clearly do not.

Genomic sciences will undoubtedly offer many new treatment opportunities. However, such opportunities are likely to apply to more selected patient populations than is the case for current therapies. This means that scientific opportunity and economic constraints are working against each other. Under these circumstances, it becomes very important to understand the nature and the magnitude of the economic problem that big pharma companies are facing when they discover and develop new drugs. In this study, we have therefore used the recent and current figures for R&D costs released by pharmaceutical industry associations, as well as some realistic assumptions for pre-marketing and production costs, to establish a discounted cash-flow model for the investment in a new drug and to define break-even points for new drugs.

Stage	Research				Development					L	Marketing									
Year	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Annual R&D expenses (nominal)	17	17	17	17	17	17	70	115	137											
Total R&D expenses		34	51	68	85	102	172	287	424											
Future value of R&D expenses		35	55	77	100	125	205	336	500	540										
Non-R&D costs (nominal; 14% disc.)									200	228										
Total costs at launch										768										
Beginning 'R&D debt' (14% disc.)										768	856	885	827	715	542	253	0	0	0	0
Sales										20	100	200	250	300	400	400	400	400	400	400
Net sales										17	80	160	200	240	320	320	320	320	320	320
Ending 'R&D debt'										751	776	725	627	475	222	0	0	0	0	0

Figure 2. *Computation of break-even points. A hypothetical example of a hospital market with peak sales of $400 million is shown. Net sales were annually deducted from the combined total of discounted R&D expenditures and discounted non-R&D costs. The resulting number is the remaining R&D debt (ending 'R&D debt'). For the subsequent year, this number is discounted with 14% (beginning 'R&D debt') and next year's net sales are deducted again. This computational cycle is repeated for each year until the remaining 'R&D debt' is zero (break-even in year 16) (Abbreviation: L, launch).*

Discounted cash-flow model

The discounted cash-flow model used here assumes that research costs occur during years 1–4, development costs occur in years 5–9 and the product is launched in year 10. Peak sales are reached in year 15 (Figure 2). Nominal R&D costs have been discounted annually with 8% (safe rate) resulting in the future value at the time of launch in year 10. The published figures for launching a new compound ($54, $125, $231, $359 and $500 million) represent the sum of out-of-pocket expenses and opportunity costs. Because interest rates of 8% or 9% have been used by all authors, we took these published figures to reflect fully capitalized R&D costs in year 9. Commercial costs incurred before launch as well as the future value of R&D costs were discounted at a rate of 14% annually. The distribution of R&D costs over the time period of nine years was modeled to reflect the typical pattern of spending during research and development; it is not meant to reflect the spending pattern of any particular drug. The figures include the costs of failures.

Non-R&D costs (i.e. commercial costs before launch of product) are also built into the model. These costs include pre-marketing costs, capital costs for production facilities, costs for outcome studies and costs of goods produced. Outcome studies are performed in parallel to clinical trials and their costs are considered as an 'add on' to R&D expenditures. Capital costs for production facilities vary with the nature of the compound, but these costs can be significant for recombinant proteins as well as for small molecules that require several steps of chemical synthesis. The model assumes that the entire non-R&D costs occur in the last year of R&D activity (year 9).

Sales were expected to increase gradually and reach a peak in year 15. Commercial costs [cost of goods (COG) and marketing and distribution costs] were deducted from sales each year, resulting in annual net sales. COG was postulated to be 15% of sales. Marketing and distribution costs in general practice (GP) markets were assumed to be 15% in years 10–15, and thereafter 5% of sales. In hospital and niche markets these expenditures were assumed to be 5% and 2.5% of sales, respectively. Table 1 shows the assumed annual net sales in the GP, hospital and niche markets.

Computation of break-even points

In the cash-flow model, net sales were annually deducted from the combined total of discounted R&D expenditures

Table 1. Net sales in various markets for which different commercial costs are assumed.

Market	Peak sales[a]	Year 10 (launch)	11	12	13	14	15	16	17	18	19	20
GP[b]	800	35	70	280	420	490	560	640	640	640	640	640
GP[b]	600	35	70	210	280	350	420	480	480	480	480	480
GP[b]	400	14	70	140	175	210	280	320	320	320	320	320
Hospital	500	40	80	160	240	320	400	400	400	400	400	400
Hospital	400	17	80	160	200	240	320	320	320	320	320	320
Niche	300	41	82	124	165	206	247	247	247	247	247	247

[a]Peak sales are assumed to be reached in year 15.

[b]In the GP market, lower marketing costs were assumed after year 15; as a result net peak sales in this market are reached in year 16.

and discounted non-R&D costs. The resulting number is the 'virtually remaining R&D debt'. For the subsequent year, this number is then discounted with 14% and the next year's net sales are deducted again. This computational cycle is repeated for each year until the 'virtually remaining R&D debt' is zero (Table 2). The year in which zero debt is reached is called the 'year of break-even'. It should be noted that royalties to third parties and non-operational costs, such as taxes, have not been taken into account in the model.

Table 2. Computation of break-even points. Accumulated and discounted R&D and non-R&D costs[a] minus net sales (in $ million)[b,c].

Year R&D costs	non-R&D costs	Market	Peak sales	10 DC	10 DC–NS	11 DC	11 DC–NS	12 DC	12 DC–NS	13 DC	13 DC–NS
500	200	GP	800	768	733	836	766	873	593	676	256
		GP	600	768	733	836	766	873	663	756	476
		GP	400	768	754	860	790	901	761	868	693
		Hos	500	768	728	830	750	855	695	792	552
		Hos	400	768	751	856	776	885	725	827	627
		Ni	300	768	727	829	747	852	728	830	665
500	0	GP	800	540	505	576	506	577	297	339	0
		GP	600	540	505	576	506	577	367	418	138
		GP	400	540	526	599	529	603	463	528	353
		Hos	500	540	500	570	490	559	399	455	215
		Hos	400	540	523	596	516	588	428	488	288
		Ni	300	540	499	569	487	555	431	491	326
400	200	GP	800	660	625	713	643	733	453	516	96
		GP	600	660	625	713	643	733	523	596	316
		GP	400	660	646	736	666	759	619	706	531
		Hos	500	660	620	707	627	715	556	634	394
		Hos	400	660	643	733	653	744	584	666	466
		Ni	300	660	619	706	624	711	587	669	504
300	100	GP	800	438	403	459	389	443	163	186	0
		GP	600	438	403	459	389	443	233	266	0
		GP	400	438	424	483	413	471	331	377	202
		Hos	500	438	398	454	374	426	266	303	63
		Hos	400	438	421	480	400	456	296	337	137
		Ni	300	438	397	453	371	423	299	341	176

[a]Non-R&D costs are commercial costs before launch, after launch commercial costs are directly substracted from sales.

[b]Table 2 shows the computation of selected examples.

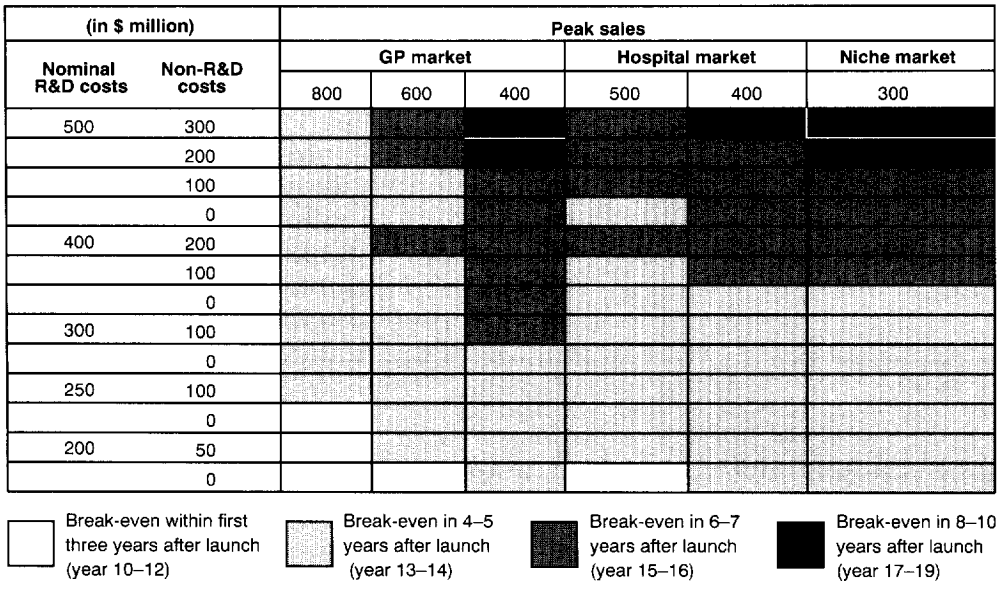

Figure 3. *Relationship between development costs, peak sales and resulting time periods within which drugs will break even. R&D costs were assumed to range between $200 and $500 million. Non-R&D costs (see text) were hypothetically set at $0, $50, $100, $200 and $300 million. Sales of $800, $600 and $400 million were studied for the GP market, for the hospital market sales of $500 and $400 million were calculated.*

Table 2 (continued).

14		15		16	
DC	DC–NS	DC	DC–NS	DC	DC–NS
292	0	0	0	0	0
543	193	0	0	0	0
790	580	661	381	434	114
629	309	352	0	0	0
715	475	542	222	253	0
758	552	629	382	435	188
0	0	0	0	0	0
157	0	0	0	0	0
402	192	219	0	0	0
245	0	0	0	0	0
328	88	100	0	0	0
372	166	189	0	0	0
109	0	0	0	0	0
360	10	11	0	0	0
605	395	450	170	194	0
449	129	147	0	0	0
531	291	332	12	14	0
575	369	421	174	198	0
0	0	0	0	0	0
0	0	0	0	0	0
230	20	23	0	0	0
72	0	0	0	0	0
156	0	0	0	0	0
201	0	0	0	0	0

[c]Abbreviations: DC, discounted costs; DC–NS, discounted costs minus net sales in the year indicated; GP, general practice market; Hos, hospital market; Ni, niche market.

Results of analysis

The summary of the results of this analysis is depicted in Figure 3. The figure is built on R&D costs of $500, $400, $300, $250 and $200 million. Peak sales of $400, $600 and $800 million were analyzed for the GP market, $400 and $500 million for the hospital market, and sales of $300 million were included for niche markets. In interpreting the figure, break-even within the first three years after launch should be considered to be an exceptional opportunity, break-even within four to five years after launch to be the accepted norm and a break-even occurring six or more years after launch to be problematic. Applying these standards, it becomes clear that at the highest R&D costs for a new compound of $500 million only drugs for the GP market that reach peak sales of at least $800 million annually are attractive, if non-R&D costs do not exceed $300 million. With non-R&D costs up to $100 million, $600 million peak sales seemed to be acceptable. A peak sales level of $400 million in the GP markets can only be regarded as a rewarding opportunity if the R&D costs can be kept below $300 million. However, R&D costs of $300 million combined with non-R&D costs not exceeding $100 million for a drug that achieves peak sales of $400 million in the GP market allow for break-even only within 6–7 years after launch. Such drugs would therefore not be considered good opportunities.

It is startling, however, that hospital peak sales of $400 million – a figure that until ten years ago seemed very attractive – can no longer be regarded as a good opportunity if

Table 3. Projected sales based on patient numbers[a]

Patient number	Patients qualifying for drug treatment (% of patient number)	Patients receiving drug treatment (% of patient number)	Market penetration for drug	Patients treated with drug	Projected sales[a]
1,000,000	50%	25%	50%	125,000	$375 million
			20%	50,000	$150 million
			10%	25,000	$75 million
10,000,000	50%	25%	50%	1,250,000	$3.7 billion
			20%	500,000	$1.5 billion
			10%	250,000	$750 million

[a]Assuming treatment costs of $3,000 per patient per year.

calculations are based on R&D costs of more than $300 million and non-R&D costs of $100–200 million. If one assumes $500 million to be the real figure for discovering, developing and launching a new compound, the minimal peak sales to be derived from the hospital markets must exceed $500 million. In the GP market the range beyond $600 million may be attractive. If the projected sales figures that represent viable commercial opportunities today are compared with the actual worldwide sales figures of existing drugs[11], the cutoff line for $800 million sales and higher lies between a drug ranked 26th in 1996 worldwide sales [albuterol (Ventolin®), Glaxo Wellcome] with $831 million, and erythropoietin (Procrit®, Johnson & Johnson), which ranked 27th. The cutoff line for $600 million sales is between the drugs ranked 39th [ondansetron (Zofran®), Glaxo Wellcome] and 40th [tamoxifen (Nolvadex®), Zeneca]. If $400 million sales are assumed to represent the critical order of magnitude, the drug ranked 64th [finasteride (Proscar®); a drug for benign prostatic hypertrophy marketed by Merck] is found to be just above this limit ($405 million) and azithromycin (Zithromax®; a modern macrolide antibiotic marketed by Pfizer) to be just at or slightly below this limit.

Morbidity, market penetration and sales

Sales that are generated today by drugs that have been launched and developed in the past provide a very inaccurate comparison for development of drugs that are judged today on the basis of financial expectations for the future. It is probably more reliable to express the problem in terms of morbidity figures and market penetration. If it is assumed that, of any given patient population, 50% qualify for any drug treatment, that 50% of those who qualify are actually treated and that a new drug to be launched in this market can have market penetrations of 50%, 20% or 10% (which would then reach 12.5%, 5% or 2.5% of the total patient population), it is possible to estimate the number of patients that would represent an attractive commercial opportunity.

The projected sales figures derived from patient populations of 1 million or 10 million, respectively, using the above market penetration figures are presented in Table 3. In this calculation, annual treatment costs of $3,000 are assumed. Within these constraints, a patient population of 1 million would barely suffice to support a positive development decision. Of course, if the treatment costs are increased to $10,000 per year, a level of commercial viability can be attained if sales reach at least 12.5% of the patient population; according to the above assumptions, this would equate to 50% market penetration. A patient population of 10 million would warrant a positive development decision in all categories of market penetration. We are aware this argument is built on some rather arbitrary assumptions: some breakthrough drugs do not only show a high market penetration, they actually *create* markets. Therefore, even a figure of 50% market penetration, representing access to 12.5% of the total patient population, may be too pessimistic. On the other hand, there are cases where the share that an innovative drug can take from a given disease market (for instance hypertension) are much lower than 12.5% of the total patient population. It is not suggested that there exists any sharp cutoff point for taking positive or negative development decisions. It is, however, suggested that the efficacy and safety hurdles that new compounds must overcome in order to elicit a positive development decision are becoming prohibitively high. Drugs that had little trouble in obtaining the green light for progressing into development ten or even five years ago may well be rejected now.

The repertoire of diseases that the big pharmaceutical companies consider worthwhile targets for improved or

even totally novel drug therapy is shrinking. If we apply historical figures of the market penetration and realistically achievable market shares of new drugs, diseases with an average prevalence of 1 million or even more cases per year may not always offer viable choices for drug development – at least not by big pharmaceutical companies under the present technological and economic conditions.

Discussion

Drug discovery, like many other scientific endeavors, is subject to scientific opportunity on the one side and economic constraints on the other. While genomics and complementary technologies will increase the number of strategies and approaches that can be taken to cure diseases, the rising costs of developing a drug appear to endanger the realization of this therapeutic potential. This discussion will deal briefly with some hypothetical solutions to the problem.

Revising new drug development

The process of drug development as practised today may have to be fundamentally revised. There is no obvious recipe for changes that can significantly reduce development costs without jeopardizing present standards of drug safety and efficacy. However, certain new patterns of development have emerged in context with the provision of drugs that are urgently needed by certain patient populations: a broad, though perhaps preliminary, acceptance of surrogate markers that are logically linked to clinical end points of a disease could speed up development and help to reduce costs. The acceptance of controlled pivotal studies that are entirely based on quality and scientific merit, and not on the nationality of the medical centers involved, would also help.

Compensating mechanisms

Such general approaches to make development cheaper will require a concerted action by industry, regulatory authorities (governments) and academia. However, there is some hope for improvement short of such fundamental solutions. Although genomics will provide many new targets for drug interventions – targets that are likely to be more disease-specific – compensating mechanisms may come into play. On average, a specific treatment will mean smaller patient populations. If development costs do not fall, this subdivision of patient populations and 'markets' may reach a critical level at which it is no longer feasible to develop a drug that is appropriate for only a fraction of patients with, say, diabetes type II or hypertension. If, however, the therapy provided is much more effective, safer and closer to the causes of a particular disease, market penetration and drug compliance will both be influenced positively. Also, this 'new type' therapy will – at least initially and at least for serious diseases – be able to command high prices. All of these mechanisms would mitigate the danger brought about by selectivity and limitations on the size of patient populations.

Profiling patient populations

There may be an additional compensating factor – already responders and non-responders to a given drug can be classified on the basis of certain metabolic patterns. It must be expected that in the future these distinctions will be carried much further. It will become increasingly possible to define those groups of patients likely to respond to a drug and those who are not. Conceptually, clinical trials could become more precise and therefore cheaper if genetic non-responders could be excluded from such studies on a regular basis.

Common denominators

Beyond the general perspective that development costs may eventually be reduced and will not continue to be prohibitive barriers to the development of important drugs, there is yet another possibility that may mitigate the conflict between the scientific solutions that are possible and those that can be economically afforded: genotypes underlying certain diseases may be different but they may be functionally interdependent or they may depend on a common denominator. Rick Lifton has pointed out that very different biochemical mechanisms that cause hypertension and relate to different genotypes seem to have a common final pathway – the epithelial sodium channel[12]. We tend to think of a genome as an egalitarian society of genes, but there is ample evidence that genes are not all 'created equal' and in their totality may reflect a rather complex system of hierarchies (Figure 4). If several disease genotypes that overlap or are totally distinct from one another have to go through common genetic/biochemical pathways to produce a particular disease phenotype, then this common pathway could provide the definitive target for dealing with all or at least several genotypic configurations. Admittedly, the resulting therapy would not represent the highest degree of selectivity for each subset of a disease, but it could

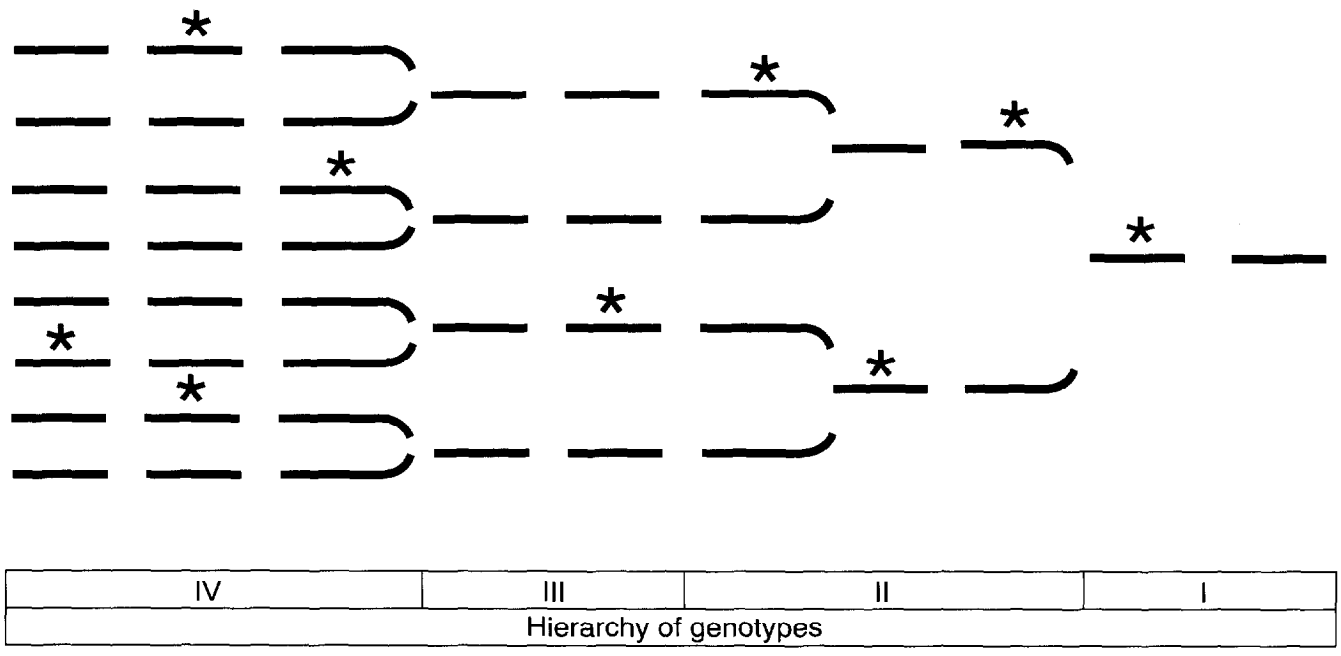

Figure 4. *Schematic map of biochemical pathways and their individual components, some of which represent genotypes associated with a particular multifactorial disease (*). All components of a given pathway are potential targets for drugs treating this particular disease. The highest hierarchy level of genotypes relating to a disease phenotype represents the broadest association of a particular biochemical event or structure with a disease. Conversely, a target within a pathway which occupies a low level in the hierarchy of genes will only be useful for a limited patient population. Without knowing the biochemical pathways as illustrated here, the genotypes (*) associated with a multifactorial disease cannot be sorted into hierarchies of genotypes. To what extent such hierarchies exist and how many 'levels of command' there may be is uncertain.*

help to reconcile scientific opportunities and economic constraints.

Genomics and other sciences are proliferating and constantly providing new perspectives and possibilities for drug research. In principle, therefore, there is no reason to be pessimistic. Every human endeavor has to deal with economic constraints – drug discovery is no exception. The escalating development costs, however, are a cause for concern. The purpose of this study has been to quantify the limitations that are already imposed on the development of new drugs by R&D costs, to show that the promise of genomics may be affected by this mechanism and to suggest perspectives that may offer at least partial relief from this problem.

ACKNOWLEDGEMENTS

We thank Dr Balbir Singh for helpful discussions and comments.

REFERENCES

1 Drews, J. (1996) *Nat. Biotechnol.* 14, 1516–1518
2 Drews, J. and Ryser, S. *Nat. Biotechnol.* (in press)
3 Drews, J. in *The Genetic Basis of Human Disease: Proceedings of the Scientific Symposium, October 2–6, 1996 in Basel* (*Ex Libris Roche*), Blackwell Science (in press)
4 Mossinghoff, G.J. (1995) *Drug Inf. J.* 29, 1077–1099
5 Schwartz, H. (1997) *Scrip Magazine* March, 15–16
6 DiMasi, J.A. *et al.* (1991) *J. Health Econ.* 10, 107–142
7 Hansen, R.W. (1979) *The Pharmaceutical Development Process: Estimates of Current Development Costs and Times and the Effect of Regulatory Changes* (*Issues in Pharmaceutical Economics*) (Chien, R.I. *et al.*, eds), Lexington Books
8 Wiggins, S.N. (1987) *The Cost of Developing a New Drug* Pharmaceutical Manufacturers Association, June, Washington, DC, USA
9 *Sustaining Innovation in US Pharmaceuticals: Intellectual Property Protection and the Role of Patents* (January 1996), The Boston Consulting Group
10 Vasella, D. (1997) *Nat. Biotechnol.* 15, 485
11 *Med. Advertis. News* (May 1996) 15 (5), 21–22
12 Lifton, R. in *The Genetic Basis of Human Disease: Proceedings of the Scientific Symposium, October 2–3, 1996 in Basel* (*Ex Libris Roche*), Blackwell Science (in press)