CIMA

Final Level

Management Accounting – Case Study

15 *FLCS*

This booklet contains the ***pre-seen case material*** for the May 2001 examination.

This booklet is ***not*** identical to the one that you have been using to prepare for this examination.

The narrative (pages 2 – 7) is exactly the same.

Appendices A, H, I J and K are also the same.

Appendices C, D, E, F and G have been revised: they now include the financial information given in the pre-seen material ***and new data for the years 1999 and 2000***. The new data has been shaded so that you can see easily what has been added.

Appendix B has been revised to include data for 1999 – May 2001.

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READ THE NEW INFORMATION BEFORE YOU ATTEMPT THE QUESTION

Contents of this booklet:

PROTON QUEST: A BIOTECH GROUP

1. BACKGROUND AND STRUCTURE

Proton Quest and its two main divisions – introduction

Proton Quest, a European biotechnology (biotech) group, was founded in 1989 and obtained a listing on a European Stock Exchange in 1994. It was founded by the current Chief Executive Officer (CEO), Dr Martin Hislop, and his former biochemistry tutor, Professor Sergio Martinez.

Proton Quest is unique in that it does not seek independently to discover or develop drugs; rather it manages networks of university and commercial partners to develop the discovery of new compounds. In short, Proton Quest is a typical biotech company in its embryonic stage, experiencing identical challenges to those facing the industry as a whole.

Proton Quest has three quite striking features. First is its close links with academia. Second, the group has two main divisions (see *Appendix A*): Molecular Allies and Techno Insights. The purpose of the Molecular Allies division is to identify innovative discovery projects; it brings together and manages virtual teams of scientists from universities and pharmaceutical companies to co-develop individual projects. As for Techno Insights, it holds a leading position in software development for drug discovery. Third, Proton Quest is unusual in the European biotechnology sector in having achieved a net profit in 1998.

Software development

The group was originally established to develop and market software to manage the drug discovery process. [The drug discovery process is briefly outlined in *Appendix K (Table One).*] Computer technology had become increasingly important in the discovery of new drugs in the late 1980s. Its importance has been crucial during the 1990s and will continue into the twenty-first century.

Informatics[1] is particularly important to the future of the pharmaceutical sector. Jan Leschy, the CEO of (then) SmithKline Beecham, commented at a public lecture at City University in June 1998, that informatics, along with molecular and genetic diagnostics, are key to the future of both his group and the industry as a whole. At the heart of Proton Quest's current range of software products are Bio-informatics, Chemo-informatics and Computer Aided Molecular Design, which are central to the informatics revolution (see *Tables Two* to *Four* in *Appendix K* for more details).

Proton Quest has been described by some analysts as the Microsoft of the drug discovery sector. It certainly has ambitions to become the industry standard in this sector and has developed a considerable established base inside both pharmaceutical and biotechnology companies. Dr Hislop recently observed that:

"We {Proton Quest} want to make our software and services the industry standard through close alliance with large international partners" (press quotation) and *"You would be hard pressed to find any pharmaceutical research establishment anywhere in the world that does not have Proton Quest software at some level"* (Top Five Consultants' report, 1998).

In fact, the group has developed many of its software products through on-site development with leading pharmaceutical companies.

Success in software is only one aspect of Proton Quest's goal to be an industry standard. The other critical aspect is provision of drug services. It is to this end that, in 1995, Proton Quest

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[1] For the purpose of this case, we define informatics as the application of computer tools to the drug discovery process. Proton Quest's tools aid researchers in the identification of targets to deal with an illness, in the process of finding "lead compounds shown to be active against a biological target" and in the process of refining a lead into a compound which enters regulatory clinical trials (*Annual Report 1997*).

formally established its Molecular Allies division. This division brings together a diverse range of skills which it offers, under contract, to pharmaceutical and biotechnology companies. The goal of this division is to play a central role in the strategic development of the group "by winning and managing drug discovery projects" (*Annual Report 1997*).

Market for outsourced specialist drug discovery IT (software) and drug discovery research services

Table A

Market	*1996 Euros, millions (€m)*	*2002 Euros, millions (€m)*	*% Growth*
Outsourced IT	500	1,300	160
IT outsourcing available to Proton Quest	400	1,000	150
Outsourced drug discovery research projects	900	2,200	144
Total accessible market	1,300	3,200	146

Source: *Proton Quest Annual Report 1997*

2. MOLECULAR ALLIES DIVISION

The importance of the division

The Molecular Allies division is of critical importance to Proton Quest, and is viewed by the head of this division, Dr Leonardo Vieira, as the future of the group. Also, the Techno Insights division is vitally important to Molecular Allies.

An intriguing aspect of the Molecular Allies division is that while it only had seven full-time staff by the end of 1997, it generated sizeable proportions of the group's revenues in 1996 and in 1997. This is despite the fact that Proton Quest employed 175 people in 1997 (*Annual Report 1998*). A share price graph (*Appendix B*) depicts the level of investor confidence in Proton Quest.

An important reason for interest in the Molecular Allies division is that it has long-term potential. Not only is there a built-in profit margin in each contract, there is also a profit-sharing element. If a drug, which the division was involved in discovering, makes it to the marketplace, the customer is required to give Proton Quest a small royalty payment on each sale. In the case of the Techno Insights (software) division, products are sold to customers at a once-off profit margin. Commenting on the software division, Dr Vieira observed that:

"As far as I am aware there are no deals done that involve royalties on drugs that may reach the market. So they develop software and sell software products for a good deal."

The Molecular Allies division has aroused interest because of its long-term potential to generate not only one half of the group's turnover, but also presents the possibility of achieving considerable royalty payments. This would be bottom line revenue and, while the royalty would be a single percentage point, it could still represent a sizeable return. As Dr Vieira noted:

"If you find a new asthma treatment or a new obesity treatment, which is something we are working on for a current client, you are talking at least a billion (one thousand million) Euro drug, so a few per cent is a few tens of millions of Euros."

The group believes that it can obtain a considerable share of the outsourced research market. Dr Hislop stated that:

"Proton Quest believes that the market for outsourced services {both IT and research} could reach €2,200 million each year within 5 years. Proton Quest, in a synergistic alliance with its

recently established partners, Molecules4U Combinations Ltd and Molecules4U Drug Discovery Ltd, is well placed to take a significant share of this market" (Annual Report 1998).

According to a press report, Dr Hislop is aiming for Proton Quest to capture between 15% to 20% of the total outsourcing market, which he predicts will have grown to ε5,000 million by the year 2005. This would equate to corporate-wide sales of between ε750 million and ε1,000 million each year. On the other hand, if Dr Vieira's prediction – that Molecular Allies will make up half of the group's revenues within three years – occurs, then this division would have increased its turnover to between ε375 million and ε500 million each year by 2005.

The group believes that to attack the biotech market effectively, it is essential to move forward on both the software and services fronts. The *1997 Annual Report* states that the overall strategic intent of the group is:

"To be the world's leading supplier of drug discovery solutions through the integration of information technology and drug discovery services including combinations chemistry, high throughput screening and genomics".

Molecular Allies – business methodology

The Molecular Allies division seeks to integrate multiple forms of knowledge from within Proton Quest, its network of partner companies, and university research sub-contractors to deliver high-value, knowledge-intensive, drug discovery services to pharmaceutical and biotechnology companies. In the context of Proton Quest, this division is of particular importance because of the rapid internal growth predicted by Dr Vieira, the size of the potential external market, and the low levels of staff required relative to turnover. The group's strategy for Molecular Allies is developed through alliances, for example, one alliance has been formed with a large Japanese pharmaceutical company, Ionic Tiger, and another with a small, virtual, UK biotechnology group, BioCell3.

The division has engaged in many major drug discovery projects. Nine of these projects (for which there are details) are outlined in *Appendix H*. An important question to ask is "why do such companies choose to outsource part of their research to Proton Quest?" In the case of the small biotechnology companies, the answer is simple. It is because of a lack of financial, or physical, resources and/or a lack of technical, or organisational, capabilities. As Dr Vieira put it:

"A small biotech {comes to us} because they don't have the know-how to do {a particular element of the discovery process} internally and they don't have the cash to buy in that know-how internally at their current resource level. They don't want to spend money on hiring somebody full time and buying a computer and software to do it. It is cheaper to come to us and they can get to the next stage of the discovery process more quickly."

The reasons why a large pharmaceutical company would be attracted to the Molecular Allies division are more complex. It is not a question of a large pharmaceutical company lacking knowledge about rational drug design, combinations chemistry, high throughput screening, or management of projects across universities and commercial organisations. Large pharmaceutical companies have all these skills, and where there are gaps in their knowledge pools, it would be possible to buy them in, given their vast financial resources. Many of the larger companies spend over ε1 billion per year on research and development. Instead, Dr Vieira identifies three broad reasons. The first two reasons essentially conform to the concept of strategic focus, while the third conforms to the concept of technology options.

The first is "spill-overs". A unit within the pharmaceutical company may have an area which it wishes to research, but because of other projects, it lacks time to commit internal resources to the project.

Second, there are technological gaps which the pharmaceutical company is aware of and decides it needs to fill. These may be specialist techniques which the company needs in order to complete a single project, or alternatively which it needs to acquire and absorb into its future drug discovery methodologies. To this end it may seek out a specialist group, such as Proton Quest, from which it can fill the gap for a single project, and/or engage in technology transfer. Examples of this kind

of collaboration would be the Panda Pharmaceuticals and Ionic Tiger projects where the Molecular Allies division is not only managing the project, and providing specialist drug discovery services such as computer aided molecular design (CAMD) and combinations chemistry, but is also enabling these capabilities to be transferred to its clients through intensive reporting and on-site training of the customer's staff.

Third is the search for new technologies. Essentially, the large pharmaceutical company engages in a diverse range of alliances to explore new and emerging drug discovery technologies and methodologies. Technology is moving very quickly and can be costly to implement. Through these alliances, the pharmaceutical company is able to see the technology or methodology in action and then decide whether it needs to develop this capability internally, or whether it is peripheral to its strategic focus and can therefore be outsourced. When referring to these types of technology search alliances, Dr Vieira commented that the pharmaceutical company:

"will want to hedge its bets and make sure that it goes for the right approach {technology or methodology} and that is another reason for making sure that it allies with someone like our group {which is involved at the frontiers of rational drug design, combinations chemistry, and high throughput screening}."

So, essentially, collaborators choose Proton Quest to fill gaps in their technological capabilities, with the aim of applying these to an individual project, or engaging in technology transfer.

The division's performance

Essentially there are three interconnected levels of success for the division. The first is that the project attains its underlying scientific goals. These goals will have been determined at the start of the project, though they may develop through a process of negotiation with the collaborative partner during the evolution of the project.

Having achieved the basic scientific goals of the project, the second and third routes of success are essentially outside the control of Proton Quest and are in the hands of the client. The second route of success is to take a compound from discovery into drug development. Drug development is an expensive process and for many reasons a client may decide not to enter a compound into clinical trials. These reasons may not be because of a failure in the project on the part of Proton Quest. As Dr Vieira notes:

"{To enter clinical trials you need} a compound that is not just active and selective, but has also got all the usual animal-type properties. There are lots of different levels of success for us. A partner's failure doesn't mean that we have failed."

The third route of success is where a drug makes it through the discovery and development processes and into the marketplace. In this scenario Proton Quest, through the division, would obtain single-figure royalties. When considering this possibility, Dr Vieira remains mindful that the basic route of success for the group remains attainment of the underlying goals of the initial discovery project. He comments that:

"If we meet our goals in a project, and that may be more than just designing an active compound, then it is a success for us. There is another tier of success, where we get a drug to market and we get a nice big royalty stream."

So has Proton Quest been successful to date?

On the first route of success the answer is yes. Collaborative partners are consistently paying Proton Quest research fees for the work it does on their behalf. They would not do so if the Molecular Allies division did not meet the scientific goals of the project.

On the second route the group also seems to have had some success. Its collaboration with RXRibo on a radio-immunotherapy product was a success at the discovery stage. The product is now in phase II clinical trials. Given that the discovery phase can take many years (Parexel International (1996) estimated that on average it takes 3·3 years), it is not surprising that few of the division's projects have entered clinical trials to date. There should be a clearer picture of the

success of the division in discovering compounds which enter clinical trials after a period of several years has elapsed.

It is probably fair to say that the long-term success of the division depends on managing projects which enter clinical trials. After all, the remit of the division is drug discovery and the immediate goal of that process is to discover compounds which can then enter clinical trials. The third route, namely a drug entering the market, is not as critical to the long-term success of the group. The reasons why a drug can fail clinical trials are varied, and where these can be managed they are largely in the hands of the developer, not the discoverers.

The financial success of the division (*Appendices F* and *G*) is masked in Proton Quest's unpublished accounts by the consolidation of the results of both the Techno Insights and Molecular Allies divisions. As noted previously, the Molecular Allies division is delivering a significant proportion of the group's turnover, while consuming only a small number of the group's internal staff resources.

Strategic direction – Molecular Allies

Unlike most of the entrepreneurial life science companies listed on European stock exchanges, Proton Quest does not directly invest shareholders' funds in the independent discovery of novel therapeutic compounds. As outlined earlier, it seeks to provide services to other companies in the pursuit of this activity. Provision of software services is one route. The other is a more direct, hands-on, participation in the drug discovery process, through provision of managerial or specialist services.

The Molecular Allies division can provide customers with specialist technical services such as protein analysis, antibody engineering, high throughput screening and quantitative structure activity relationship services – to mention but a few. These projects are normally of a short duration and are aimed at over-stretched drug design departments within pharmaceutical companies which are looking to sub-contract specific projects, or companies that currently do not have access to these types of skills and expertise in-house (source: *Proton Quest).*

The Molecular Allies division can also service higher level bespoke research projects in which it plays both a managerial and technical role. These projects may be initiated by either the customer or Proton Quest (or its divisions). For example, in the case of collaboration with Ionic Tiger Pharmaceuticals, it was Molecular Allies which came up with the initial novel drug target, focusing on Ion channels. It then sold this initial idea as a project to Ionic Tiger. Molecular Allies manages the project on Ionic Tiger's behalf in return for contract fees, milestone payments[2], and a share of future royalties. In the case of its collaboration with BioCell3, it was BioCell3 which came to Proton Quest with a novel drug target. It contracted the group to manage a project to identify and optimise lead compounds which BioCell3 could then take into clinical trials. Again, Molecular Allies receives research fees, milestone payments and future royalties.

In such projects, the Molecular Allies division brings with it a "wealth of experience and expertise in target identification, screening, synthesis, molecular design and informatics" (*Annual Report 1997*). More importantly, it brings with it a network of contacts through which it can access the skills of leading edge researchers. There are two strands to this network. The first is access to university researchers. This is a key element of the division's original guiding principle.

3. PROTON QUEST'S PARTNER COMPANIES

The second important network is Proton Quest's two partner companies, Molecules4U Combinations Ltd and Molecules4U Drug Discovery Ltd. The results of these two partner companies are dealt with as trade investments in the accounts. Dr Hislop sums up the importance of these strategic partners, noting that:

[2] Milestone payments involve a collaborative partner making staged cash payments upon the achievement of specific research milestones.

"The combination of Proton Quest's software and drug design expertise, Molecules4U Combinations' chemical synthesis skills and Molecules4U Drug Discovery's advanced screening capabilities will provide customers with a highly cost-effective method of accelerating the drug discovery process" (Proton Quest).

Proton Quest has built up its expertise in drug discovery software through internal growth and over a dozen acquisitions. These acquisitions have brought with them new products, markets and expertise. (The Molecular Allies division seems to be emulating this strategy to a lesser extent, concentrating more on organic growth and its web of university sub-contractors.) Nevertheless, during 1997, Proton Quest was involved in establishing Molecules4U Combinations Ltd (see *Appendix I*) and Molecules4U Drug Discovery Ltd (see *Appendix J*), taking a minority stake in both companies, with options to buy outright.

The central importance of these companies in the long-term success of the Molecular Allies division is stated in the *1998 Annual Report*. It notes that if the group is to achieve its aim of being a full drug discovery service provider, then it is important that it should have four core capabilities, namely informatics, chemical libraries, biological screening and genomics.

Informatics is the central capability around which the others are presently organised. This capability has been internally developed by Proton Quest. The *1997 Annual Report* notes that the Proton Quest group provides the essential informatics infrastructure that co-ordinates the scientific team. The Molecular Allies division provides multi-disciplinary research project management and expertise in lead identification and optimisation.

Expertise in chemical synthesis and combinations chemistry libraries is provided by Molecules4U Combinations. Expertise in biological screening is provided by Molecules4U Drug Discovery.

The final key capability is genomics. When discussing the impact of genomics in a press interview, Dr Hislop predicted that about 60% of the new drugs targets will emerge from these disciplines.

Clearly this is an area which the group needs to address in the near future.

4. FURTHER CONSIDERATIONS

A major threat to the commercial success of small biotechnology companies, identified in a *Top Five Consultants' Report*, is that of technology consolidation. The report warns that companies relying on a single technological expertise will have grave difficulty in continuing to attract pharmaceutical partner companies, from which they can extract high profit margins. However, the Molecular Allies division has successfully expanded its technological expertise in informatics to a broader range of technological capabilities through its virtual network. The future of the division appears bright if it can build on its current technological capabilities, manage its network, and expand its technological base to include a genomic capability.

APPENDICES

Contents

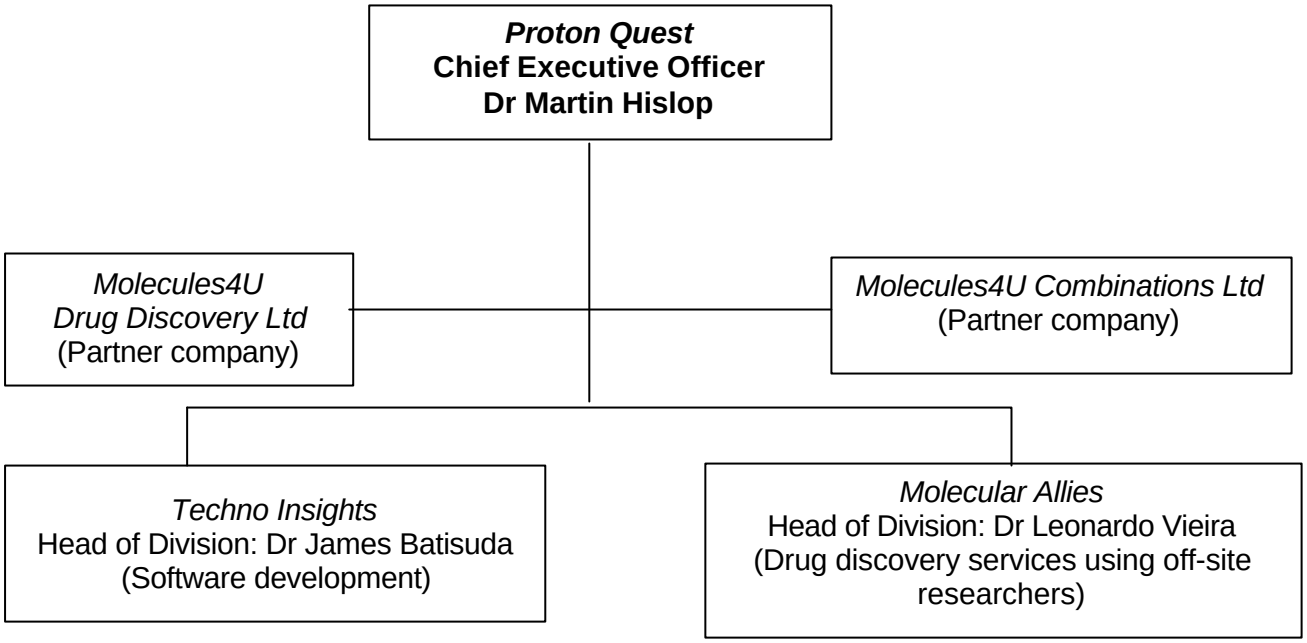
Note:

Appendices C – G comprise unpublished accounts.
They combine the financial information given in the pre-seen material with new data for the years 1999 and 2000. The information for those two years is shaded.

Appendix A

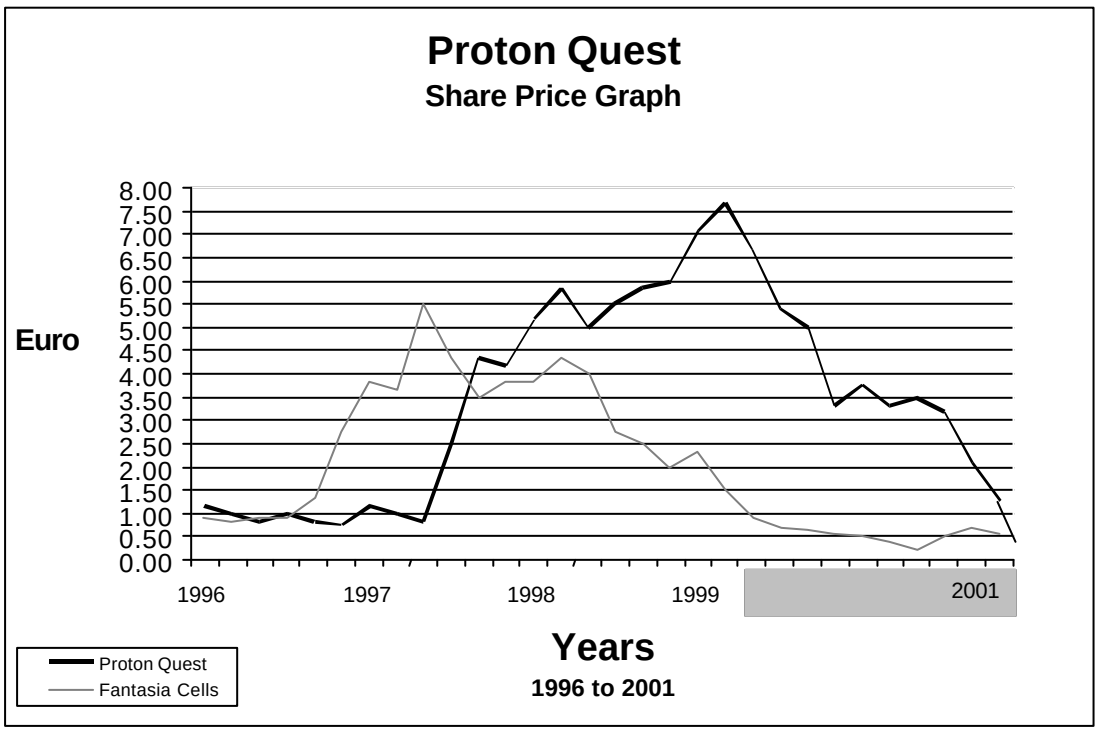
PROTON QUEST DIVISIONAL CHART

Divisions, Directors and Partner Companies



Appendix B

Proton Quest Group share price graph for the period January 1996 to May 2001.



Note: Fantasia Cells is a comparable company

Appendix C

Proton Quest
Balance sheets at 31 December 1996, 1997, 1998, 1999 and 2000

Unpublished Group Accounts

These accounts include all of Proton Quest's activities

	1996 Actual £000	*1997 Actual £000*	*1998 Actual £000*	*1999 Actual £000*	*2000 Actual £000*
Fixed assets:					
Tangible assets	1,033	1,923	2,327	6,617	8,312
Intangible assets	0	0	0	32,488	22,473
Trade investments	0	0	9,263	8,665	4,293
	1,033	1,923	11,590	47,770	35,078
Current assets:					
Stock	262	208	73	267	453
Debtors	3,868	4,293	10,367	19,467	14,502
Investments	1,170	1,038	0	0	0
Cash at bank and in hand	4,998	13,392	32,612	12,138	5,965
	10,298	18,931	43,052	31,872	20,920
Less: Current liabilities:					
Trade creditors	1,552	1,400	1,455	2,625	4,488
Finance leases	112	75	65	50	1,855
Other creditors	1,793	397	988	1,565	1,925
Accruals and deferred income	4,432	4,680	7,448	10,260	14,730
Bank overdraft	0	0	0	780	0
Deferred cash consideration	0	0	0	0	145
	7,889	6,552	9,956	15,280	23,143
Net current (liabilities)/assets	2,409	12,379	33,096	16,592	(2,223)
Total assets less current liabilities	3,442	14,302	44,686	64,362	32,855
Less: Creditors due after one year	132	160	25	757	3,645
Provision for liabilities and charges	0	0	0	0	9,020
Net assets	3,310	14,142	44,661	63,605	20,190
Called-up share capital	19,843	53,140	107,265	129,700	129,728
Reserves	(16,533)	(38,998)	(62,604)	(66,095)	(109,538)
	3,310	14,142	44,661	63,605	20,190

Candidates should not attempt to reconcile the movement in reserves.

Notes:

1. The change in intangible assets in year 2000 is because of an impairment charge and amortisation of goodwill.

2. The two partner companies began their relationship with Proton Quest on 1 January 1998.

Appendix D

Proton Quest
Profit and loss accounts for the years ended 31 December 1996 –2000 (unpublished)

These accounts include the trading operations of Molecular Allies and Techno Insights

	1996 Actual e000	*1997 Actual e000*	*1998 Actual e000*	*1999 Actual e000*	*2000 Actual e000*
Sales	10,298	16,315	26,068	35,842	32,933
Cost of sales	(3,513)	(4,188)	(5,388)	(6,135)	(8,325)
Gross profit	6,785	12,127	20,680	29,707	24,608
Research & Development	(2,898)	(5,227)	(8,237)	(11,037)	(12,428)
Administrative expenses	(10,450)	(10,767)	(13,655)	(22,127)	(32,055)
EBIT (earnings before interest and tax)	(6,563)	(3,867)	(1,212)	(3,457)	(19,875)
Interest income	505	877	1,667	1,555	315
Interest expense	(97)	(92)	(28)	(145)	(388)
EBT (earnings before tax)	(6,155)	(3,082)	427	(2,047)	(19,948)
Taxation payable	(112)	(208)	(192)	(838)	262
Earnings after tax	(6,267)	(3,290)	235	(2,885)	(19,686)

Appendix E

Proton Quest
Statement of cash flows 1996 – 2000 (unpublished)

These accounts include the trading operations of Molecular Allies and Techno Insights

	1996 Actual e000	*1997 Actual e000*	*1998 Actual e000*	*1999 Actual e000*	*2000 Actual e000*
EBIT (earnings before interest and tax)	(6,563)	(3,867)	(1,212)	(3,457)	(19,875)
Interest income (expense)	408	785	1,639	1,410	(73)
Pre-tax profit	(6,155)	(3,082)	427	(2,047)	(19,948)
Taxes	(112)	(208)	(192)	(838)	262
Net income	(6,267)	(3,290)	235	(2,885)	(19,686)
Depreciation	480	653	823	1,640	4,432
Amortisation	0	0	0	1,700	10,015
Capital expenditures	(913)	(768)	(950)	(1,867)	(5,253)
Residual cash flows	(6,700)	(3,405)	108	(1,412)	(10,492)

Appendix F

Molecular Allies
Profit and loss accounts for the years ended 31 December 1996 – 2000 (unpublished)

These accounts are prepared on the same basis as **Appendix D**

	1996 Actual £000	*1997 Actual £000*	*1998 Actual £000*	*1999 Actual £000*	*2000 Actual £000*
Sales	3,591	5,053	7,110	10,003	14,075
Cost of sales	(1,229)	(1,822)	(2,703)	(4,010)	(5,948)
Gross profit	2,362	3,231	4,407	5,993	8,127
Research and development	0	0	0	(80)	(232)
Administrative expenses	(2,510)	(3,432)	(4,681)	(3,258)	(9,313)
EBIT (earnings before interest and tax)	(148)	(201)	(274)	2,655	(1,418)
Interest income	79	136	259	242	50
Interest expense	(15)	(14)	(4)	(23)	(62)
EBT (earnings before tax)	(84)	(79)	(19)	2,874	(1,430)
Taxation payable	(45)	(85)	(78)	(341)	107
Earnings after tax	(129)	(164)	(97)	2,533	(1,323)

Appendix G

Molecular Allies
Statement of cash flows 1996 – 2000 (unpublished)

These accounts are prepared on the same basis as **Appendix E**

	1996 Actual £000	*1997 Actual £000*	*1998 Actual £000*	*1999 Actual £000*	*2000 Actual £000*
EBIT (earnings before interest and tax)	(148)	(201)	(274)	2,655	(1,418)
Interest income (expense)	64	122	255	219	(12)
Pre-tax profit	(84)	(79)	(19)	2,874	(1,430)
Taxes	(45)	(85)	(78)	(341)	107
Net income	(129)	(164)	(97)	2,533	(1,323)
Depreciation	75	102	128	255	689
Amortisation	0	0	0	264	1,557
Capital expenditures	(142)	(119)	(148)	(290)	(817)
Residual cash flows	(196)	(181)	(117)	2,762	106

Appendix H:

Molecular Allies Division – publicly announced projects

Collaborator / Partner	*Project*	*Start year*	*Details*
BioCell3	(Multi-disciplinary discovery)	1996	Proton Quest (PQ) does in-house design work and outsources chemistry and biology to university researchers.
Panda Pharmaceuticals	(Combinations library designs & synthesis)	1997	PQ provides molecular modelling techniques to design novel targeted combinations libraries which Molecules4U Combinations will synthesise. An important aspect of this collaboration is the training and transfer of technical skills to Panda staff.
Immune2Day	(Antibody humanisation)	1995 to 1997	Immune2Day got exclusive rights to the antibody technology. PQ got payment and rights to use Immune2Day's antibody technology outside of the latter's specialist field, oncology.
Transform-Motif Corp	(Drug design & combinations chemistry)	1998	PQ and Molecules4U Combinations will "identify novel lead compounds for the treatment of metabolic disorders" *(Proton Quest)*.
RXRibo	(Computational – antibody humanisation)	1993	Humanised antibody component of a radio-immunotherapy product to localise antibodies at tumour sites. The drug is now in phase II clinical trials.
Medical Sylapion	(Drug design, combinations chemistry & HTS)	1998	PQ will use its software and discovery skills to design multiple libraries. Molecules4U Combinations will provide synthesis of the libraries. Molecules4U Drug Discovery will provide High Throughput Screening (HTS) and consultancy services for Medical Sylapion's internal discovery process.
Bonded Sol	(Computer Aided Molecular Design : CAMD)	1997	PQ to provide drug design services to enable Bonded Sol to develop a blood growth factor free of third-party patent hindrances.
Cascade Org	(Computer Aided Molecular Design : CAMD)	1996	Targeting drugs to treat cancer. Cascade Org contributes HTS of chemical libraries and directed drug design methods.
Ionic Tiger	(Multi-disciplinary discovery)	1996	Discovery of a novel drug candidate, based on Ion channels with the potential to target multiple diseases. The project is managed by PQ, with much of the work outsourced to university researchers.

Source: *Proton Quest press releases*

Appendix I:

Molecules4U Combinations Ltd (private, unlisted partner company)

Foundation

The company was founded in January 1998 by a group of top scientists and professors from two leading universities. In 1998, Proton Quest invested ε2 million for a 19.99% shareholding. The other shareholders are the senior management, including Eric Smyth, CEO (a former colleague of Dr Martin Hislop, CEO of Proton Quest) and Molecules4U University, which provided intellectual property rights. This is a trade investment.

Technology

The company takes a medicinal chemistry approach to drug discovery, providing chemical synthesis services. It specialises "in the design, production and supply of chemical structures for the drug discovery industry" (*Proton Quest*). It can produce "moderately sized libraries of up to 20,000 compounds in a pure, well-characterised reproducible form. Milligram batches of each component in a library will be produced at the same time to provide the end user with sufficient material for every stage of testing" (*Proton Quest*). Such libraries play a crucial role in generating a pool of compounds from which novel lead compounds can be identified.

Commercial offering

Combinations chemistry services, consultancy, and technology transfer.

Collaborative relationship with Proton Quest

Molecules4U Combinations plays an important role in Proton Quest's long-term aim of providing one-stop shopping for drug discovery services. This goal requires four capabilities, two of which are chemical synthesis and combinations libraries (*Annual Report 1998*). The Molecular Allies division manages projects which identify novel drug targets to which Molecules4U Combinations' technology can be applied to generate a library of potential lead compounds. In turn, Proton Quest's (and partners') capabilities in screening chemical libraries and rational drug design enable these leads to be optimised before entering clinical trials.

Deals to date

Molecules4U Combinations has combined with the Molecular Allies division in three important alliances. The first aims to provide combinations library designs and synthesis, including technology transfer, to Panda Pharmaceuticals. The second alliance is with Medical Sylapion. This is targeted on "carbohydrate processing enzymes which have potential therapeutic use for diseases such as fungal infections" (*Proton Quest*). Molecules4U Combinations provide syntheses of libraries, which are designed using expertise from Proton Quest, while the libraries are screened by Molecules4U Drug Discovery. The third collaboration seeks to "identify novel lead compounds for the treatment of metabolic disorders" for Transform-Motif Corp.

Appendix J:

Molecules4U Drug Discovery Ltd (private, unlisted partner company)

Foundation

The company was founded in January 1998 by four leading scientists. ε8.2 million was raised from investors, primarily Proton Quest, which invested ε6.0 million: ε3.3 million in return for a 19.99% shareholding, and ε2.7 million in preference shares. If Molecules4U Drug Discovery is floated, or sold, then the preference shares convert into a 10.1% shareholding. Proton Quest has the option, exercisable between the years 2000 and 2002, to purchase the remaining ordinary shares for the greater of 3 times turnover, or 15 times net profit. This is a trade investment.

Technology

High Throughput Screening (HTS), the company's core technology, enables researchers to screen libraries of molecule compounds against biological targets (such as proteins) to determine how potentially potent, selective and bio-available the compounds are as a new drug candidate. Biological screening, using HTS, is central to the task of identifying novel lead compounds.

These libraries can contain millions of compounds, hence automation is essential in the screening process. Molecules4U Drug Discovery has invested in robotics systems which enable the company to "screen up to 100,000 compounds a day from customers' own libraries of chemical compounds against either novel or non-proprietary targets" (*Proton Quest*).

Commercial offering

The company can screen libraries for customers in addition to the design of chemical assays and HTS consultancy.

Collaborative relationship with Proton Quest

Many of the company's products will be sold via collaborative projects with Proton Quest. Third-party sales will be through Proton Quest's distribution system, for which Molecules4U Drug Discovery pays a percentage of the overheads. As outlined in Proton Quest's *Annual Report (1997)*, HTS is one of the four capabilities needed to achieve the group's goal of becoming a one-stop-shop provider of drug discovery services. The Molecular Allies division manages projects which identify novel drug targets to which Molecules4U Drug Discovery's HTS technology can be applied to generate lead compounds. In turn, Proton Quest's capabilities in rational drug design enable these leads to be optimised before entering clinical trials.

Deals to date

The Molecular Allies division of Proton Quest, in co-operation with Molecules4U Drug Discovery and Molecules4U Combinations, is managing a drug discovery programme targeting fungal infections for Medical Sylapion. Molecules4U Drug Discovery will screen the libraries which Proton Quest designs and develops, with Molecules4U Combinations conducting the synthesis of those libraries.

Appendix K

Additional information

INDUSTRY BACKGROUND
The pharmaceutical industry and the context within which Proton Quest operates

Modern biotechnology came to life with the discovery of DNA (deoxyribonucleic acid), which can be simply thought of as the blueprint of life (BIO, 1999). Three advances made the manipulation of DNA, and hence modern biotechnology, a practical reality. These were hybridoma technology, discovered by Kohler and Milstein in 1975 *(Faulkner, Senker, and Velho, 1995)*, Recombinant DNA (rDNA), discovered by Boyer and Cohen in 1973 at Stanford University *(Faulkner, Senker, and Velho, 1995)* and Protein Engineering *(Oxender and Graddis, 1991).*

Further advances in molecular biology have enabled companies to gain a much greater understanding of biological organisms and how they can be manipulated to improve human health, crop yields and environmental protection. The application of modern biotechnology spans four important sectors in the world economy, namely:

- discovery and development of therapeutic drugs to improve treatment of human diseases;
- diagnostics tools to identify human and animal diseases;
- agricultural biotechnology, which involves the genetic modification of plants and animals with the goal of improving yields and nutrition; and
- environmental protection, such as clean up of hazardous wastes *(BIO, 1999; Ernst and Young, 1999).*

Although the importance, in terms of potential contribution, of biotechnology to our society is immense, this industry, especially in the European sector, is still in its embryonic stage. As a result, many companies which comprise this sector are many years away from significant revenues generated by sales of drugs. For example, until recently there was only one biotechnology company in the UK approved for marketing a drug: that is, Chirocaine, by Celltech-Chiroscience. With a lack of real earnings to fund R&D expenditures, independent biotechnology companies in Europe have relied primarily on two sources of cash. These sources consist of *(i)* funds raised from stakeholders, and *(ii)* revenues raised through collaborative agreements, with equity funding being the primary source of capital for companies in their early stage of development. Although for biotechs the amount of capital raised via stakeholders has declined in the US over recent years, it has risen in Europe, thus suggesting the perceived importance of the European biotechnology sector.

Appendix K (continued)

Table One:

The drug discovery process

The goal of the drug discovery process is to create a drug compound, targeted at a specific disease, which can enter regulatory clinical trials. Should the drug successfully pass through the regulatory process, then it can be marketed. At the heart of the Proton Quest approach to drug discovery is an embrace of both traditional drug discovery and computer-based rational drug design. The difference between the two approaches is that rational drug design seeks "to model the molecular structure of the target of a drug, and then design a drug molecule which will fit it. This contrasts with the alternative, which is to screen a large number of compounds for drug activity, choose the most promising and make a whole lot of variants, choose the most promising of them and repeat until a suitable drug is found" *(Bains 1993).*

In practice, it is not possible to create a drug compound employing computer methods alone. Thus, Proton Quest offers its customers a combination of software to facilitate rational drug discovery, in addition to managerial skills and experience in the blending of this technique with traditional methods of screening and discovery.

There are four broad stages to a drug discovery process, three of which Proton Quest is actively involved in. The first is the identification of a **target disease.** Targets may be selected on the basis of specialist knowledge about the disease within a company, the potential market rewards of pursuing a treatment, and/or new advances in technology which offer potential application in a targeted disease area. Targeting a disease is generally the domain of Proton Quest's clients.

Second is **identification of biological targets.** These are proteins or genes which the researchers believe play an important role in the spread of the target disease. The researchers seek to understand what form of compound would be needed to interact with the protein or gene which is causing the disease and thus manage or cure it.

Third is **lead compound identification.** This involves identifying compounds which are biologically active against the biological target.

Fourth is **lead optimisation**, or **refinement.** Having identified a number of biologically-active compounds, it is necessary to determine which of these has the best mix in terms of activity, with the lowest level of toxicity.

Table Two:

Bio-informatics – the identification of biological targets

"Bio-informatics is the use of software, databases and on-line resources to store, retrieve and analyse genomic information (such as information on human genes). Analysis of genomic information enables suitable biological targets to be identified in order to discover new drugs which may halt the disease or control the infection" (*Proton Quest Annual Report 1997*).

Bio-informatics software produced by Proton Quest is used by researchers as "tools for the analysis of DNA and protein sequence data" *(Proton Quest).* Bio-informatics tools play a central role in the **identification of biological targets.**

Appendix K (continued)

Table Three:

Chemo-informatics – the identification of lead compounds

Chemo-informatics builds upon the process of identifying biological targets (central to which is Bio-informatics) with the goal of **identifying lead compounds**.

Chemo-informatics software tools enable researchers to "capture, analyse and communicate the increasing volumes of biological and chemical data available in the search for new lead compounds and drug candidates" *(Proton Quest Annual Report 1997).* These tools are used for "selecting, comparing, relating, mining data for databases of chemical compounds, structures, properties and biological assay results" *(Proton Quest).*

Examples of Chemo-informatics software available from Proton Quest include RS^{3} ™ Discovery (which is used for "storing, searching and retrieval of chemical structures in addition to chemical and biological properties, experimental data and registration" *Proton Quest)*, and DIVA ™ (a spreadsheet-based product to facilitate the visualisation and analysis of chemical structures).

Table Four:

Computer Aided Molecular Design (CAMD) – lead optimisation

Lead optimisation involves analysing the compound to discover its potential biological activity and toxicity. When a lead compound is identified, it still remains to be proven whether this compound can be safely applied to humans, and whether it successfully tackles the disease. The compound may well need to be structurally modified to enable it to combat the disease both safely and effectively. Once the researchers have modified the lead compound, it must then be entered into clinical trials before it can be marketed. These trials can cost hundreds of millions of Euros. If the compound fails in trials, then it cannot be sold to the public. It is, therefore, vital that the process of lead optimisation discovers potential problems with the compound, and solves them prior to entering into clinical trials. CAMD greatly enhances the efficiency and effectiveness of the lead optimisation process when compared to older, conventional screening techniques.

"In the past this {lead optimisation} involved random chemical synthesis around a particular lead structure with known, but inadequate, biological properties. …. {CAMD} allow{s} a more rational approach whereby a research scientist can visualise a compound's structure through molecular modelling and explore structural modifications to improve its desired properties" *(Proton Quest Annual Report 1997).*

CAMD tools are "used both by computational and experimental chemists to predict reaction mechanisms and explain interactions, speeding up the identification of compounds with desirable properties". *(Proton Quest)*

Table 5:

Genomics

Genomics is the identification of the genetic basis for disease, which relates to the information encoded by DNA. The study of genomes, which includes genome mapping, gene sequencing and function, is often linked to the search for genes which are associated with disease.

15

FLCS

Management Accounting – Case Study

Pre-seen material

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