

### **Japan in Focus: Strategies for Innovation and Global Drug Development What Differentiates Japanese Pharma Companies from their Western Counterparts?**

For some years innovation in pharma R&D has emanated from the United States, Europe and Japan. However, since the mid 1990s times have been difficult for Japanese pharmaceutical companies but there are some recent signs of beneficial change.

#### **Background**

##### *Cost Containment*

- For three successive years there has been a reduction in the reimbursement price of pharmaceuticals, an increase in co-payment by patients, and a change in the involvement of doctors in the dispensing systems which may all have been a disincentive to focus on the home market. In addition, the poor growth in sales has made it difficult for Japanese companies to increase their R&D budgets to the same extent as Western companies.
- Because of their predominantly domestic focus, Japanese companies have suffered as a result of changes in the Japanese economy and a slowly-growing pharmaceutical market. However, the ageing Japanese population may support some market growth in the future but is also likely to drive the government into health care reform and further cost control relating to the medicines bill with pharmaceuticals representing over 20% of healthcare expenditure in 1998.

##### *Research and Development*

- The average R&D budgets of the top 10 Japanese companies are about one-fifth of the average of the top 10 Western companies. (Japanese companies have a higher level of licensed-in and joint research products in clinical development than their Western counterparts.)
- It has been suggested (Anon, 1999a) that Japan has a firmer science base in chemistry than pharmacology and this may be influencing the direction of innovation by Japanese pharmaceutical companies. (However, there has been a backlog of products waiting to enter the Japanese market.)

##### *Mergers and Acquisitions*

- Japanese companies, on the whole, appear to have so far escaped the wave of mergers and acquisitions which has passed through Western companies. However, there has been a steady process of dissolution of major marketing alliances with Western companies throughout the 1990s.

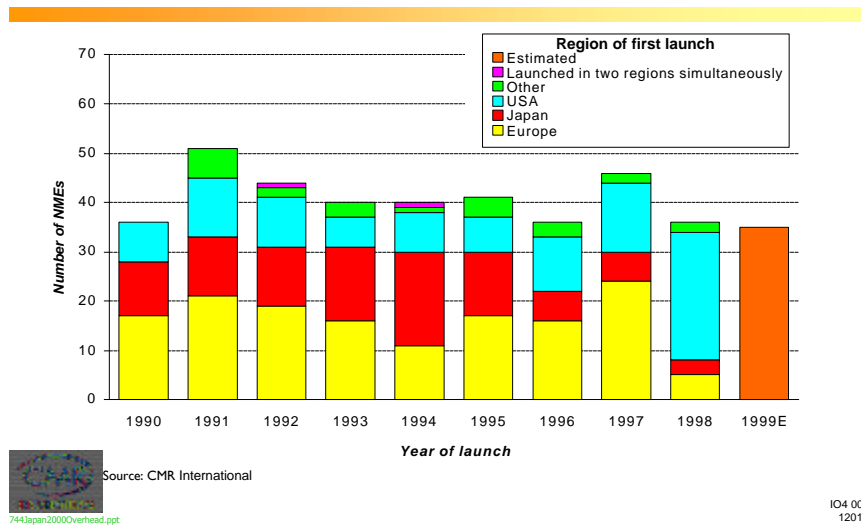
Until the late 1990s conditions for the pharmaceutical industry in Japan had differed from those faced by Western companies with the industry operating to different requirements. There had been a need for extensive and disparate clinical studies on Japanese subjects, the regulations for Good Clinical Practice had been less rigorous than those in leading Western countries, and price controls were unlike those in most Western nations. Price provisions which were previously favourable to “me-too” products were amended in 1996 in a manner which would reduce the likelihood of their introduction.

The Japanese pharmaceutical market, valued at \$44billion is the second largest national market in the world after the USA and Europe (Anon, 1999b). The industry, in common with many others in Japan, suffered from the decline in the Japanese economy which started in the early 1990s. There has been a fall in the number of New Molecular Entities brought to market in Japan since 1994. Although the Japanese market is now growing, that growth (6%) was only half the rate of growth of pharmaceutical markets of North America and the UK, which grew by about 12% in 1999 (Anon, 1999b).

Because of the difficult situation in their domestic market, a number of leading Japanese companies have expressed a need to globalise, but there have been questions about the industry’s commitment to globalisation (Maurer, 1997).

## Japan's Position as a Premier Centre for New Introductions Has Been Lost

### New molecular entities first launched worldwide 1990-1999E

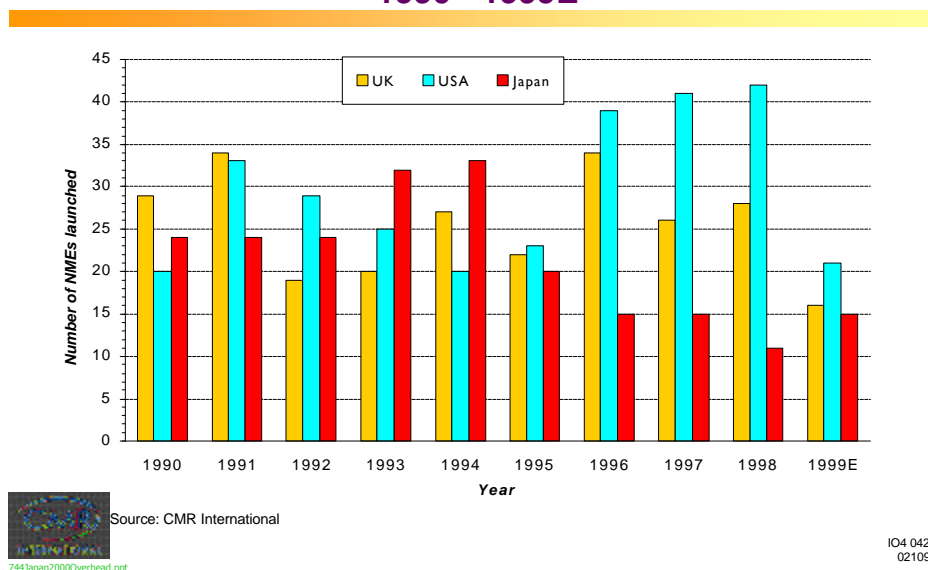


“In the near future, I am sure, Japan will re-emerge as one of the world’s drug development centres, enjoying an influx of excellent drugs...”  
Dr Doi, Councillor for Pharmaceutical and Medical Safety, MHW, CMR International Workshop 1999

- The number of first launches in Japan exceeded those in the other major countries before 1995.
- After 1995 there were, on average, fewer first launches in Japan than in each of the other major regions. This fall was accompanied by other indications of reduced activity. A decline in patenting activity of about 25% by the Japanese pharmaceutical companies occurred in 1997 (Anon, 1997). This decline may be a consequence of the general economic conditions in Japan although there have also been difficulties within the patenting system.

### Falling Entries to the Japanese Market

### Number of NMEs launched in the UK, USA and Japan 1990 - 1999E

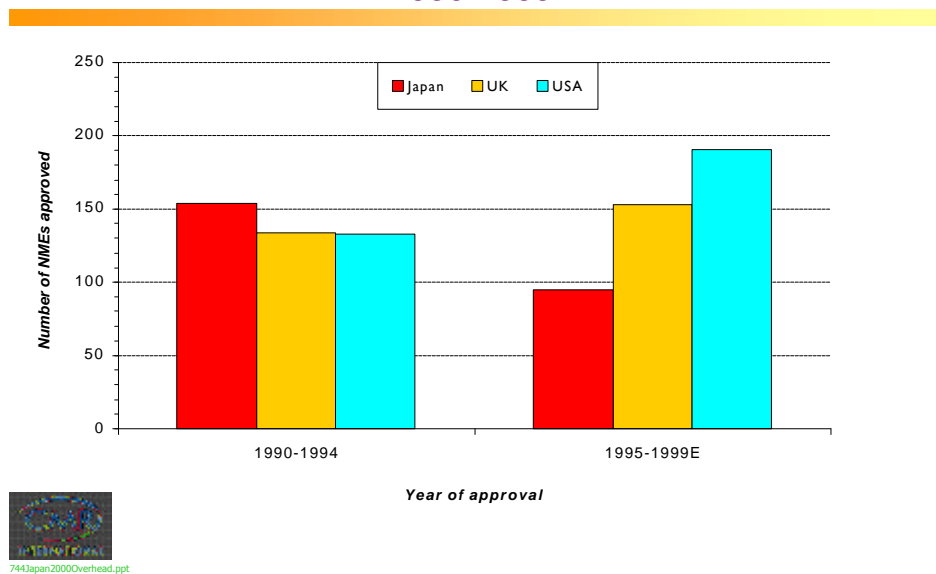


- The aggregate number of launches in Japan was greater than those launched either in the UK or the USA from 1990 to the end of 1994, but less from 1994 to the end of 1998. After 1994, launches in Japan halved whilst those in the USA increased markedly.

- Launches in Japan by foreign companies and transnational joint ventures (nearly all of which involved Japanese companies) were much the same in 1990-1994 as in 1995-1998, but the launches by Japanese companies alone halved in the period 1995-1998.
- There were few launches by Japanese companies alone in the USA and UK in both periods, 6 in 1990-1994 and 3 in 1995-1998, but Japanese involvement in transnational joint ventures with launches in those countries increased slightly in the same periods.
- Apart from changes in the Japanese economy, it seems likely that the fall in launches in Japan is, at least in part, a consequence of delays in the regulatory approval process carried out by the MHW. Successive falls in the permitted reimbursement prices in 1996, 1997 and 1998 and increases in patient co-payments may have also had an impact on this parameter, discouraging new entries to the Japanese market.

## The Number of Approvals in Japan has Fallen Since 1994

### Number of NMEs approved in UK, USA and Japan 1990-1999E



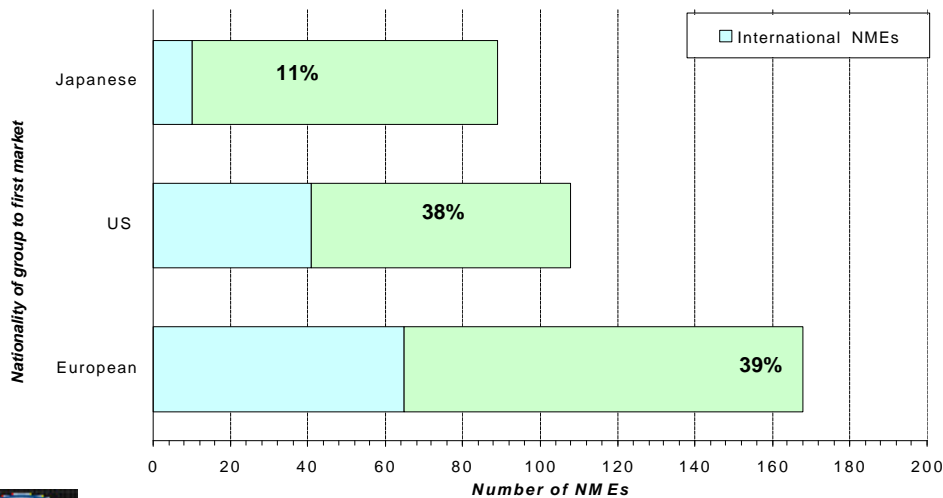
“More transparency and objectivity should be ensured in the NDA process. Both qualitative and quantitative improvements need to be made in the area of personnel involved in the review process to shorten the period required.”

Liberal Democratic Party Policy Research Council on Basic Medical Policies Subcouncil to Examine  
Pharmaceutical Policies-1998

- Since 1994 there has been a very marked fall in the number of NMEs approved in Japan. From 1990-1994 over 150 NMEs were approved in this country, compared with about 130 each in the USA and the UK. Since 1995 the number approved in Japan has fallen below 100, those in the UK increased to above 150, and those in the USA have risen to about 190.
- The fall in approvals in Japan is probably to some extent related to the performance of the Japanese regulatory authorities. In the past, in the absence of harmonisation of clinical trials requirements, there may also have been a reluctance by foreign companies to commission the additional trials considered necessary before approval in Japan. The difficulty in obtaining the highest innovation premium since the introduction of the relevant system in 1991 might have been a disincentive for innovative and foreign companies.

## Differences in Bringing Products Quickly to a Global Market

### Number of NMEs first marketed 1990-99 by European, US and Japanese marketing groups and the number reaching international status by the end of 1999



Source: CMR International

International NME: Available in 2 of the 3 ICH regions (USA, Japan, EU)

IN12 0171  
160399

“.. it has become increasingly clear that the ability to create innovative new drugs and develop these products on a global scale is the factor that will determine whether Japanese pharmaceutical enterprises will continue to grow ...”

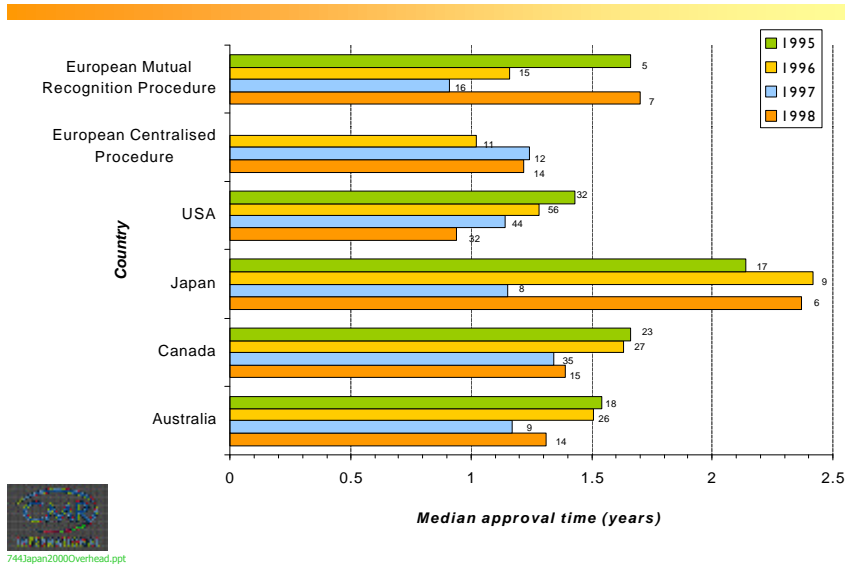
Masayoshi Onoda, President and Chief Executive, Yamanouchi Pharmaceutical Co. Ltd, Annual Report 1998

- Japanese marketing companies have achieved fewer international products\* than Western companies. In a “shrinking” world, a company’s survival will depend on its ability to globalise and bring products quickly to a global market. This may be reflected in the number of NMEs which achieve international status. Japanese marketing companies still lag behind Western companies in this respect.
- Only about one-eighth of NMEs launched by Japanese marketing companies since 1990 have become international. In comparison, more than one-third of NMEs launched by European and US companies became international.
- This lack of international NMEs may be because the leading Japanese companies have, on average, lower sales revenues than leading Western companies, and relatively few Japanese companies have their own direct sales organisations covering the whole world, with many delivering their products through licensees. It is very interesting that although about 10% of leading global medicines of 1996 were discovered by Japanese companies, only 40% of these were being marketed principally by a Japanese company (Halliday and Walker, 1999). The remaining products had presumably been licensed out or sold to other, Western companies.
- Although Japanese companies have increased the proportion of their income from foreign sales in recent years (Jack, 1999), they still lag behind US and European companies.

\*The definition of an international product is one launched onto two out of the three markets of Europe, Japan and the USA.

## Longer Median Approval Times in Japan

### Median approval times in major markets 1995-1998



Approval times for the European Centralised Procedure are taken from the EMEA application date to the Commission's decision date; for European Mutual Recognition Procedures, from the date of application to Reference Member States to the end of the 90-day discussion phase. The 'Best Practise' guide of October 1996 indicates that Concerned Member States should grant a national authorisation within 30 days of the end of the 90-day phase.

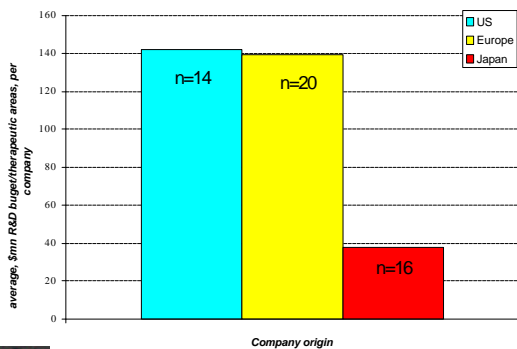
"By the end of 1999, the MHW is to have a review workforce comparative to that of European countries, and shall fulfil its internationally-made promise of shortening the review time in Japan to 12 months in the year 2000...."

Dr Doi, Councillor for Pharmaceutical and Medical Safety, MHW, CMR International Workshop 1999

- The median time for approvals in Japan in 1995 (for 17 NMEs) and 1996 (for 9 NMEs) were markedly greater than those in other leading nations or regions for which data is available.
- The median times for approvals in Japan in 1997 (8 NMEs) showed an improvement. However, the figure for 1998 (6 NMEs) has returned to the 1996 level. The apparent dip in approval times may reflect a group of compounds which had a priority status or were fast tracked. However, the MHW has indicated that its target review times will be 12 months by the year 2000.

### Japanese Companies Appear More Extended in their Research Focus in Relation to R&D Budgets than Western Companies

#### Amount of R&D expenditure per therapeutic area for top 50 companies



#### Japan

Takeda  
Sankyo  
Eisai  
Yamanouchi  
Otsuka  
Daiichi  
Shionogi  
Fujisawa  
Chugai  
Ono  
Sumitomo  
Tanabe Seyaku  
Kyowa Hakko  
Yoshitomi  
Tsumura  
Meiji Seika

#### Europe

Glaxo Wellcome  
Novartis  
Hoechst Marion Roussel  
SmithKline Beecham  
Roche  
Astra  
Rhone Poulenc Rorer  
Bayer  
Zeneca  
Boehringer Ingelheim  
Sanofi  
Schering AG  
BASF  
Merck KGaA  
Novo Nordisk  
Akzo Nobel  
Servier  
Synthelabo  
Nestle  
Solvay

#### US

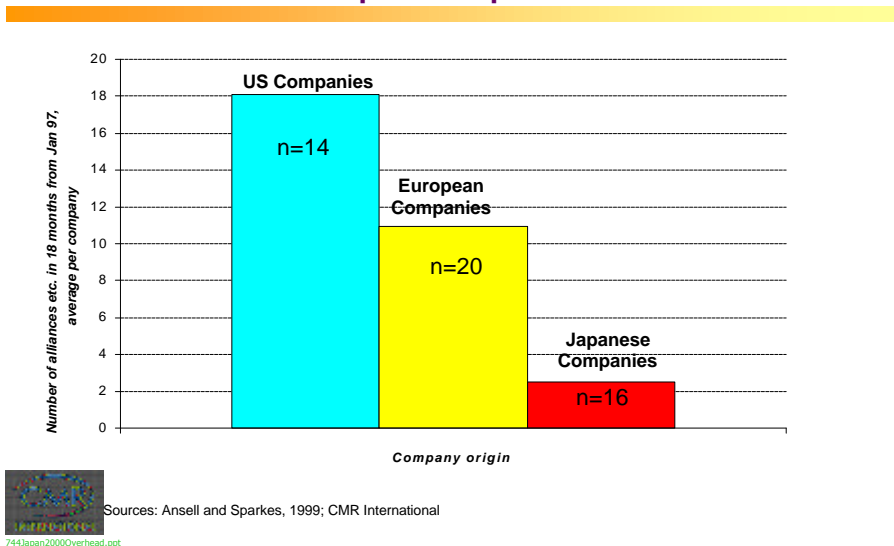
Merck & Co  
Bristol Myers Squibb  
Pfizer  
American Home Products  
Johnson & Johnson  
Lilly  
Abbott  
Schering Plough  
Warner Lambert  
Searle  
Procter & Gamble  
DuPont Merck  
Amgen  
Pharmacia & Upjohn

Sources: Ansell and Sparkes, 1999; CMR International

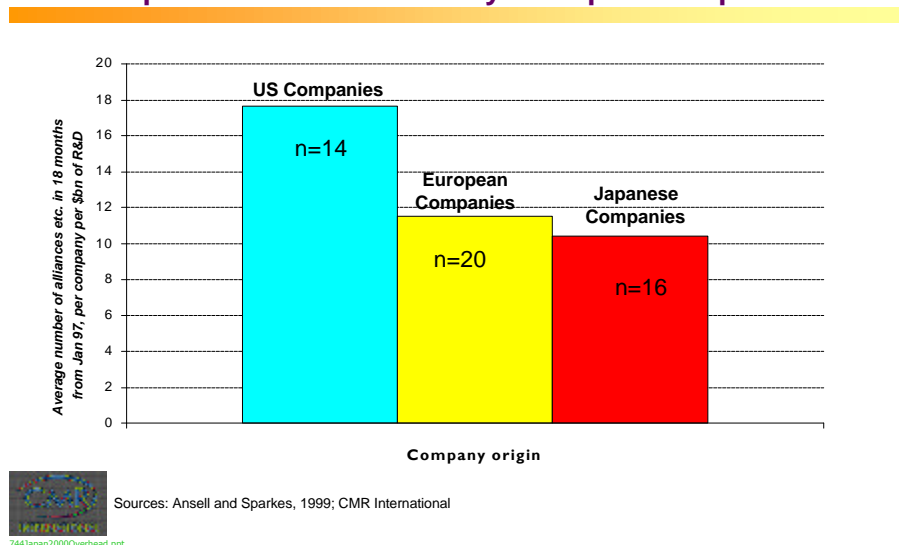
- Japanese companies are active, on average, in 6 therapeutic areas per company (Ansell and Sparkes, 1999), as many as most Western companies, although spending a correspondingly smaller amount in R&D. These levels of therapeutic focus approximate to those determined in a recent CMR International survey. (Lobo et al 1999.)
- Japanese companies have lower funding per therapeutic area of R&D activity. When the R&D budgets of companies were divided by the number of therapeutic areas in which they were active in 1998 (Ansell and Sparkes, 1999) there were distinct differences. The average value for Japanese companies (n=16) was approximately \$38mn per therapeutic area, compared with averages around four times higher, of about \$140mn for both US (n=14) and European companies (n=20).
- It has been suggested (Anon, 1999a) that budgetary constraints may make it difficult for Japanese companies to invest in the enabling technologies of genomics, high-speed chemistry and high throughput-screening; if this is so, it may place them at a competitive disadvantage.

## Japanese and European Companies Make Fewer Links than US companies

Average number of alliances per company by nationality, for top 50 companies



Average number of alliances per company by R&D expenditure and nationality for top 50 companies



“Top priorities in the pharmaceuticals company include rapidly creating new drugs that are accepted world wide, globalising its business, mainly its R&D activities; improving existing pharmaceuticals; and forming alliances.”

Hideki Yasui, President, Kyowa Hakko Pharmaceuticals Company, Annual Report 1999

- Japanese companies (n=16) made fewer alliances and technology acquisitions than US companies, but much the same number as European companies in relation to the size of their R&D budgets. Combining CMR International data and data from a survey of activity in alliances, technology acquisition and licensing over a period of 18 months from the start of 1997 (Ansell and Sparkes, 1999) it was found that Japanese companies had made an average of around 10 alliances per billion dollars of R&D expenditure. European companies (n=20) an average of 11.5 alliances per billion dollars, and US companies (n=14), an average of about 17.5 per billion dollars.
- Japanese companies (n=16) were found to have engaged in an average of 2.5 links in this period, compared with averages of nearly 11 links for European companies (n=20) and about 19 for US companies (n=14). The Japanese companies with relatively smaller R&D budgets and European companies may not be initiating the potentially large number of links needed to achieve global distribution of an NME, or sufficient links to successfully incorporate the products of new technology.

### **Inequality of R&D Budgets for Leading Japanese and Western Companies in 1998**

“In order to survive, drug companies must excel in R&D, marketing and overseas business development”  
Ippei Asai, President of Tanabe

- Leading Japanese companies have much smaller R&D budgets than Western companies.
- It is estimated (CMR International) that the top 10 Western companies invested an average of about \$1.5bn each in R&D on ethical pharmaceuticals in 1998 (total of \$15bn). Spending by the top 10 Japanese companies is estimated to be about one-fifth of that, an average of around \$0.32 bn each (total \$3.2bn)
- The inequality in R&D budgets will make competition with leading Western companies very difficult. The poor growth in their sales has made it difficult for Japanese companies to increase their R&D budgets to the same extent as Western companies.

### **The Future**

“Today, faced with the significant challenges posed by a rapidly ageing population, globalization, and the information age, the pharmaceutical industry itself is about to undergo sweeping transformations.”  
Yoshibumi Kawamura, President, Sankyo Co., Ltd- 1999 Sankyo website

Companies in the Japanese pharmaceutical industry have been challenged to demonstrate growth prospects to investors through innovative R&D and efficient marketing or end up in a downwards spiral of lost share value (Anon, 1999a). It appears that the leading companies recognise the problems they face, however there are signs of further change in their circumstances, some of them beneficial.

In 1998 the MHW set itself the target of achieving a 30% reduction in its part in the drug review process by August 2000, and intended to double the review staff by the end of 1999. Foreign clinical data became acceptable through guidelines issued in autumn 1998. These changes may result in an eventual increase in the number of NMEs introduced onto the Japanese market.

Improvements to the patenting system are being made, including the recruitment of more examiners specialising in pharmaceuticals, in order to accelerate the processing of pharmaceutical patents.

The establishment of the Office of Pharmaceutical Industry Research (OPIR) indicates the Japanese pharmaceutical industry's willingness to face and adapt to the economic, political, and social challenges it faces. OPIR is charged with creating a vision for the future of the industry and devising strategies to achieve it.

In 1996 the export to sales ratio of nine major Japanese firms was under 10% (Maurer, 1997). Takeda was the exception, achieving foreign sales approaching 22%, which by 1999, had become the average for 9 of the 10 leading Japanese companies (Jack, 1999). It has been predicted that if recent trends continue at least half of the top 10 Japanese companies are likely to have achieved a 50:50 split of sales between foreign and domestic markets by 2005 (Jack, 1999).

Although sales performance in Financial Year 1998 was poor for many Japanese companies, the Japanese market grew by 6% over the year ending August 1999 (Anon, 1999b), an improvement on the 5% value for the previous 12 months. On the other hand there is a prediction that the domestic market may fall in 2000 because of a severe official price cut (Anon, 1999a). These pressures may drive some Japanese companies into consolidation.

**“In five or six years time, if we have no new products then consolidation might be considered ...but basically I want to find a Japanese way to survival.”**

**Haruo Naito, President & Chief Executive, Eisai- reported in Financial Times, 14<sup>th</sup> June 1999**

The changes in regulators' requirements have made it easier for foreign competitors in the Japanese market reducing the need for alliances with domestic companies. If the activity of foreign companies increases this will, of course, also increase the pressures on domestic companies.

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### **Definition of New Molecular Entity:**

A new chemical entity or biological compound (including products of biotechnology) which has not been previously available for therapeutic use in man and is destined to be made available as a “prescription only medicine”, to be used for the cure, alleviation, treatment, prevention of *in vivo* diagnosis of diseases in man. New salts, pro drugs, metabolites and esters of existing compounds and certain biological compounds (e.g. vaccines and antigens) are excluded. Combination products are also excluded unless one or more of the active constituents has never been previously marketed.

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