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Rare Diseases and Orphan Medicinal Products

Helen Crompton

The graduate school of Business
Strategy and Entrepreneurship research group

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Helen P. Crompton

Graduate School of Business

The Manchester Metropolitan University Business School

Aytoun Street

Manchester

M1 3GH

Email: H.Crompton@mmu.ac.uk

Biography

Helen Crompton is a full-time PhD student with the Innovation and Entrepreneurship group. Funded by a Faculty studentship, Helen is currently researching the effects of the EU Orphan Drug Regulation (2000) on innovation in dedicated biotechnology firms (DBF's) and potential barriers to new products entering the market. Prior to joining the Business School, Helen studied at the Department of Information and Communication (MMU) for her BA Information Technology, and at PREST (Manchester University) for a MSc funded by the ESRC.

Abstract
This paper surrounds innovation as socially constructed and posits a model for innovation policy based on Mode 2 knowledge production (Gibbons et al 1984), where scientific peer review is replaced by merit review demanded by accountability to a wider social, economic and political sphere. The paper looks at scientific research into rare diseases and the strategies being adopted by biotechnology companies. The paper then introduces the EU Orphan Drug Regulation (2000) and raises concerns about the pharmaceutical industries' use of publicly funded research and patent protection. Other barriers to patients actually receiving new treatments, even if they get as far as production, are raised in the final section.

Keywords: innovation, rare diseases, patents, Mode 2, orphan drugs

1. Background

According to Perspectives on Business Innovation;
www.businessinnovation.ey.com/journal/issue4/features/welcome/body.html
20.11.00.

> 'The present pace of discovery in genetics, neuroscience and medical measurement technology guarantees that the early decades of the millennium will be defined by biotechnology and the life sciences'.

It could be argued that we are moving from an information economy to a bio-economy (Rifkin1998, Oliver 1999). Multiple technological innovations may lead to the development of new medical treatments. Established pharmaceutical companies may face increased competition from new dynamic entrepreneurial biotechnology enterprises. Advances in theory and research are needed to develop appropriate responses and provide frameworks that will influence the innovation process in the 21st Century biotechnology industry. The conceptual frameworks of National Systems of Innovation (NSI) concentrate on the supply side, ignoring consumer demand and the influence of the media upon this demand (Senker et al p2, 1999). Globalisation and multinationals render NSIs incomplete if not obsolete. According to Senker et al (p80):

> 'Controversies appear when the distribution of expertise during the innovation process does not take into account some potentially interested actors. The controversies begin when some actors who claim the right to participate to the definition of risks, costs and benefits [*the factors in technology assessment*] are not included in the management of innovation'.

According to Senker et al (1999), technology assessment includes risk, efficiency of new technologies and even the direction taken by scientific and technological research. It could be argued that social movements may prove more effective, in the analysis of technology assessment, than 'unconnected' government agencies and proclaimed 'experts'. There have been attempts to show policy- makers listen to the 'public' but, as Senker et al (p81,1999) suggest,

> ‘Consultation processes are no more than a cheap way to give the illusion of participation’ (*by the ‘public’*).

Innovation has been studied from the perspectives of social psychology, economics, business studies, sociology and science and technology studies. Collyer (1996) claims that factors in the social or technical environment are subsumed in psychology, by an emphasis on the personality structure or cognitive activity within the individual. In the area of business studies and economics the emphasis has been on the development and transfer of products to the market rather than on the creation of new products – largely ignoring inventions that have no, or limited, commercial application (like orphan drugs) where invention is left un-theorised and few studies theorise innovation itself, or in fact innovations that have ‘failed’:

> ‘In brief, these studies suppose that the ‘market’ is an entity existing separately from ‘society’; that self-interest fundamentally organises behaviour in the market; that innovations are the result of ‘technical factors’ which are inherent properties of inventions and must, by dint of their survival in the market place, constitute an improvement over existing technologies and that science and scientific principles form the basis of, and are essential precursors to technological development’ (Collyer, 1996, p9)

According to Collyer (1996) other scholars report that the level of innovation is affected by factors such as the size, structure and ownership of the firm, the existence, or competition from, other products and the relationship between the enterprise (in this case biotechnology), clients (in this case patients), government or suppliers (in this case government regulation and patients who supply their knowledge and ‘bodies’). This suggests that innovativeness is stimulated by factors internal or external to the firm. Sociological and philosophical studies recognise the market as socially constituted, as is innovation (see Collyer 1996, p10, Winner 1977). Therefore innovation is subject to, and shaped by, differing interests and hierarchies of power. Metcalfe (2000) further suggests that innovation is a ‘combinatorial explosion.’

Social studies of science and technology of the processes of technological development and diffusion (Pinch & Bijker 1984 et al) have also challenged

the technology trajectory and the linear approach to innovation. However few studies have concentrated on the social, cultural or political process of innovation, the focus being on the adoption and diffusion processes. According to Collyer (1996) most studies, which theorise the social formation of ideas and knowledge, focus on the locus of scientific knowledge production, in the research laboratory (see Knorr- Cetina 1995 in Jasanoff et al 1995, Latour 1987). These studies ignore the political and ideological influences from external sources and other sites of knowledge production (ergo Mode 2 sites in industry and for example, medical practitioners seeking solutions to practical problems, or especially in this case the patients and their advocates). In the OD 'market' we can see industry, researchers (public and private), charitable organisations (as advocates), regulators (politics) and venture capitalists brought together in a public forum.

The rapid pace of technological and scientific advances, together with the mapping of the human genome, promises more understanding of disease processes. These advances in informatics, proteomics, pharmacogenetics, stem-cell and gene therapy research show the possibilities of finding novel compounds for drugs and other therapeutic interventions (Financial Times 6.10.98) raising the hopes of people who suffer, as a minority, from rare, as yet untreated, genetic disorders. The subject is not isolated, rare diseases do not just affect the patient – families and society are affected as well. There is hope too for the future generations who either inherit diseases or carry recessive genes, that have previously bypassed his (or her) ancestors, and 'suddenly' appear, to destroy their lives. There is also the possibility of finding new treatments for common disorders:

> 'Companies that produce orphan drugs tend to be highly valued in the market because the technology platforms they create may eventually yield treatments for more common diseases'
> Jos Peeters: Vice Chairman EASDAQ (EPPOSI 2000)

There are numerous examples of research into minority diseases having benefits for majority populations, yielding insights into other more common diseases. Research on epidermolysis bullosa, a rare skin condition, laid the

ground for knowledge of the wound healing process (*www.redherring.com* 17.3.01). It was Stanley Pusiner's research into mental illness (Kure disease) in an isolated tribe, whose culture included eating the brains of deceased relatives that led to an explanation for contagion in mad cow disease. Official response, although severely delayed due to bureaucratic incompetence, may have reduced the risk of a major epidemic. The 1985 Nobel Prize in Physiology of Medicine went to researchers in homozygous familial hypercholesterolemia – a rare disease. As long ago as 1657 the English physician William Harvey, who discovered the circulation of the blood wrote:

> 'Nowhere does nature more openly display her secret mysteries than in cases where she shows traces of her workings apart from the beaten path; nor is there any better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of Nature by careful investigation of cases of rare forms of disease'.
>
> Quoted in www.redherring.com 17.3.01

According to Torrent-Farnell (2001) there are around 6,000 diseases (70-80% of genetic origin), out of the 30,000 known diseases, which are individually rare but collectively represent a significant number of patients who, at present, are an excluded minority. Rare diseases affect around 25million (7%) of the population in the European Union. The majority of sufferers are children, one third of whom will die in the first year of life. Half of the survivors may be handicapped for life with the remainder receiving some form of disease management enabling an acceptable quality of life (Torrent-Farnell, 2001). If ethnic minorities in this country were refused a service both society and civil rights groups would be offended. There is no justification, on moral grounds, to deny a 'genetic minority' the same right to health as enjoyed by the majority population.

People are becoming more demanding and politicised as they become both more educated and better informed (Rifkin 1998). New Information and Communication Technologies (ICT's), especially the Internet allows patients and their carers to obtain knowledge about their condition and (sometimes false) hopes of a 'cure'. Global communication has also led to otherwise dispersed patient groups (using informal networks and networking) to form 'virtual' interest groups (Nonakas' (1995) 'cyber-ba'). National and

international alliances have grown to advocate for their members' interests. The power and direction of influence by interest groups depends on factors such as leadership, members' attributes and resources. According to Rifkin (1998) biotechnology has created scientific controversy unparalleled in other scientific spheres. Many have argued that, in the case of biotechnology, social welfare priorities have been ignored by those in the field with commercial interests (Webster 1991). There appears to be a threat to commercial R&D from a new source of countervailing power. United lobby groups could become more powerful than unions or government. To what degree will they influence government and company policy?

2. Innovation policy for the 21st Century?

The massification of higher education, an increase in the social utility of new knowledge, an informed and empowered citizenry, greater accountability by decision makers and a broadening of research partnerships are characteristics of globalisation (Ohmae 1990) and Mode 2 research (Gibbons et al 1984). An informed and highly educated (global) citizenry (at least in the rich countries) now exists who are concerned with the impact on society of a range of techno-political controversies. Will they become central actors in the innovation process? Governments at both national and local levels are an important force in science based economic development. Gibbons et al (1984) regard the essential difference between Mode 1 and Mode 2 to be concerned with changes in the mechanisms that assess quality. A pragmatic criterion becomes important rather than abstract rational theorising and quality assessment by peer review is replaced by merit review demanded by accountability to a wider social, economic and political sphere. Mode 2 is heterogeneous in relation to the skills and actors employed, trans-disciplinary in that it cuts across conventional disciplinary boundaries and is located in a multiplicity and diversity of sites. Mode 2 recognises the complexity, non-linearity and reflexivity of knowledge production recognising that Mode 2 contributes theoretical structures, research methods and modes of practice different from mono-disciplinary regimes. Mode 2 then replaces, or transforms, established institutions, practices and policies.

An innovation model for the 21st Century could be based on Mode 2 knowledge production and a social constructionist approach. Gibbons et al (1994, p160) suggests *'It is that people in their fungibility, multicompetence and capacity to connect with others are the critical resource'* requiring an understanding of knowledge production and exchange. Ergo *'The best innovation policy is on two legs.'*

> 'As more and more aspects of life in society are perceived to involve issues having a techno-scientific dimension science cannot be left to scientists alone. The methods and techniques of knowledge production in Mode 2 have become important ways to investigate societal issues in which many individuals and groups have some stake…. Interactions between science and technology, on the one hand, and social issues on the other, have intensified. The issues are essentially public ones, to be debated in hybrid fora in which there is no entrance ticket in terms of expertise'
>
> Gibbons et al (1994).

Gibbons et al explore major changes in the way knowledge is produced. Their thesis suggests:

> 'that the parallel expansion in the number of potential knowledge producers on the supply side and the expansion of the requirement of specialist knowledge on the demand side are creating conditions for the emergence of a new mode of knowledge production' (p13).

Mode 1 is mainly to be found in basic research, mostly academic, producing scientific documentation. Mode 2 is mainly to be found in applied research, mostly industrial, producing patents through the development of applications or processes. There may be crossovers into strategic applied research by both modes but in general they are different types of knowledge production, or the mechanism by which research benefits economic growth. New (Mode 2) knowledge production, and the search for economic pay-offs, is exerting pressure on institutionalised research to change (Ziman 1994) especially within Universities and government laboratories. According to Webster (1991) biotechnology has led to an interdisciplinary mixing of specialities in a way, and to a degree never seen before. Webster also suggests that the distinction between basic and applied research no longer seems appropriate. According to

Gibbons et al (1994) researchers are less firmly institutionalised as people come together in temporary teams and networks, which may dissolve when the problem has been resolved. The resulting mosaic will be complex and tracking will be difficult for evaluators, especially in defining the boundaries between research and the environment.

Gibbons (2000) suggests that there has been an increasing public concern about issues to do with public health, the environment, communications and privacy, which have stimulated the growth of knowledge production in Mode 2.

> 'Growing awareness about the various ways in which advances in science and technology can affect the public interest has increased the numbers of groups who wish to influence the outcome of the research process. This is reflected in the varied composition of the research teams. Social scientists work alongside natural scientists, engineers, lawyers and businessmen because the nature of the problems requires it. Social accountability permeates the whole knowledge production process. It is reflected not only in interpretation, and diffusion of results but in the definition of the problem and the setting of research priorities, as well. An expanding number of interest, and so called concerned groups are demanding representation in the setting of the policy agenda as well as in the subsequent decision making process. In Mode 2 sensitivity to the impact of the research is built in from the start. It forms part of the context of application.'
>
> Gibbons (2000).
>
> http://edie.cprost.sfu.ca/summer/papers/Michael.Gibbons.html

This can be seen in the public backlash following the BSE fiasco and the concerns raised about GM crops, human cloning and the surveillance allowed by new ICTs. The government has responded to these concerns by 'public understanding of science' initiatives, the formation of numerous committees and assurances about 'open government'. Companies are responding with initiatives such as 'corporate governance' and increased funding for public relations exercises. The questions are who sits on these 'interest' and 'concern' groups. Who funds them? How 'open' are they and do they represent society

or capitalists? There are accusations (within the US orphan drug arena) of large pharmaceutical firms using their wealth to lobby politicians and of actually funding patient groups to lobby on their behalf (Love, 1999). What will be the situation under the recent EU regulation?

Today's hyper-competitive environment means that research can no longer be sanctioned under the classic scientific model but moves to Erno-Kjolhede et al's (2000) extension to Gibbons thesis, placed within the Triple Helix (University-Industry-government relations). To which I wish to add the 'customers', in this case patients who provide their knowledge and tissues for medical research.

3. Scientific Research Into Rare Diseases

> ' The network of patients, scientists and industry involved in fighting rare diseases can provide a model for European-wide research; your [referring to EPPOSI workshop 2000] collaboration is far more developed than that of other research areas. Networks, research infrastructure and private investment are essential to speed up the development of therapies'
>
> Bruno Hansen: Director, Quality of Life Programme – Directorate General of Research, EU Commission (EPPOSI 2000)

In most cases rare diseases attract attention from small networks of researchers. The vital tools for scientific research are databases, DNA and tissue collections. These tools are needed as patients with rare diseases are geographically dispersed and therefore examining them individually would present a logistical problem. Biological databases give information on genes, DNA sequences, mutations and proteins. Medical databases provide information on diseases and drugs and also give limited access to patient registers. Published articles and information on research projects are available on the Internet for both professionals and the public, although some sites are hard to navigate. An example of a database is Orphanet, which was established by the French government. It allows access to information on research projects, clinical trials, clinical laboratories, professionals and patients, including relevant web links.

Published research is publicly available. However it could be argued that research is dependant on the interests of the particular researcher or their 'sponsor'. Much research may not be done because the 'research faculty' is not interested in the research (topic). Researchers may not be able to get the research published or pursuing a particular topic may not be good for their career. Also different disciplines receive varying funding dependant on their perceived usefulness. Research may be produced together with industry for competitive advantage therefore knowledge is protected (kept secret or patented) before publication. Knowledge may also be withheld from the public due to political or social reasons. Therefore research takes place in a political, economic and social context. University scientists, who are in constant search for funds, are now adopting strategic approaches to their careers, becoming more entrepreneurial and loosening their disciplinary affiliations. The consequence is an increase in the permeability of knowledge:

> 'to the extent that the imperatives of a problem context require co-operation or networking with other practitioners, whether in industrial, governmental or university laboratories, whether nationally or globally, the hold of established modes of knowledge production is weakened' (Gibbons et al. p23)

Uhlin et al (2000) suggest that a hybrid research culture is emerging under Mode 2 which points to the role of knowledge in innovation and co-operation amongst human actors, across multiple sites, who are the repositories of this multiple competent knowledge. Matusik and Hill (1998) point out that researchers have given little attention to knowledge issues involving malleable firm boundaries, which are increasingly the norm.

The convergence of science, technology and business under Mode 2 represents a breakdown of clearly demarcated boundaries. Innovation and learning within hyper-competition will be the central rationale of new management paradigms. It is clear that different kinds of information may be necessary upon which to make sound business decisions and that the traditional organisational and management models may not apply to the emerging complex relationships between disciplines and practitioners. A mismatch between organisational capabilities and environmental demands has resulted in crisis. Crisis is a precondition for the emergence of a new theory or model.

Box 1: The strategy Framework

Science as product: To sell or licence a portfolio of R&D projects and assets, in a continuous stream, to large pharmaceutical companies - or even exit by sale of company and then a return to Academia to start another one.

Science as competence: The building of in-house competencies through cementing and expanding strategic alliances, providing consultancy services, selling on projects and expertise. The long term goal being to expand the companies portfolio and internal skills base, freeing it from resource dependencies and achieving autonomy

The independent strategy: The building up of a small biotechnology firm into a company with core technologies, able to go from R&D to production, marketing, sales and distribution creating the greatest challenge to the established pharmaceutical sector.

Source: Adapted from Rifkin (1998)

A company's strategy is dependent on its 'product' focus, the founders (entrepreneurs) focus, aims and objectives and its management style. Thus the networks established by dedicated biotechnology firms (DBFs) in informal collaborative links co-evolve with strategy (Norus 1998) and there will be a variety of approaches and network configurations from simple to complex, from informal to formal. Box 1 shows the basic strategy drivers in DBFs. The independent strategy appears to be a challenge to big pharmaceutical companies. Biotechnology companies, such as Genzyme and Serono have already produced orphan drugs for unmet medical needs. Genzyme's new treatment, used to control phosphorous levels in the blood of dialysis patients, is expected to reach sales of $140million in 2001 with around 70% margins (www.redherring.com 19.09.01). However very few companies are able to adopt the independent strategy due to a lack of resources and the risks involved in the discovery process, clinical trials and the regulatory approval of products. Big pharmaceutical companies may make an offer too good to refuse and the company may be acquired. It is perceived that DBF's do not have the resources

to bring a product through to market and reach independence, however a great deal of help is available under the OD regulation. Will this stimulate a move to the independent level? Will the established pharmaceutical companies allow this competitive threat?

Powell et al's (1996) statistical analysis of 225 firms was a study of networks and learning. The findings were that sources of knowledge are likely to be found in the 'interstices between firms', including Universities, suppliers and customers. This is similar to Gibbons et al's (1994) idea of hybridization. Hybridisation refers to the need to accomplish tasks at the boundaries and in the spaces between systems and subsystems (Gibbons et al 1984, p37). Although Powell et al (1996) and also Powell (1998) do refer to customers, in relation to network structures, they do not elucidate what is meant by 'customer' or the customer's actual contribution to networks. These studies refer to networks and organizational learning, in collaboration with a diverse set of external partners, but do not include the 'experts' (patients and carers, or patient groups that have many medical experts as members) and their collaboration and contribution to innovation (knowledge).

Networking is more prevalent in knowledge intensive firms (KIFs), where the level of technological sophistication will be 'positively correlated with the intensity and number of alliances in those sectors' (Powell et al 1998). 'Customers' (patients and clinicians) in the orphan drug arena may be an important resource to biopharm companies as they are the experts in their particular condition and provide unique knowledge, material for research and assistance (through participation) in clinical trials. Cohen & Levinthal (1990) introduced the concept of absorptive capacity, the ability of organisations to recognise the value of new external information, assimilate it and apply it to commercial ends. Innovation and organisational learning is seen as a function of a firm's access to knowledge and its 'absorptive capacity'. However the question remains, as to what new (affordable) treatments these new 'customers' actually receive in exchange for their collaboration.

4. The U.S. Orphan Drug Act (1983)

Patient groups, without effective treatments for their conditions, provided the impetus for the formation of the National Organisation for Rare Disorders (NORD) which, with the help of the media, lobbied the Federal government to assist in the development of treatments for rare diseases. This culminated in the passage of the US Orphan Drug Act of 1983 (see Crompton 2001). There appears to be an unanswered question as to whether the Act encourages innovation and if so, at what cost (Rhode, 2000).

Pharmaceutical companies follow the economic model based on the law of supply and demand (Rohde, 2000), focusing resources on the largest markets in order to achieve the greatest returns. Even if there was an indication that a compound could be used in a treatment for an orphan disease it was difficult to find a company that would take the research forward due to the cost of clinical trials and production. The mass marketplace became the driver of innovation in product development (Rohde, 2000). Recognising that unless incentives were provided the market would continue to operate on the economic model US sufferers of minority diseases used the power of mass lobbying and the media in pushing the Act, with its economic and regulatory incentives, through Congress. The passage of the Act was opposed by the pharmaceutical industry, which preferred a relaxing of FDA approval to more legislation. The Act was opposed by the US tax department, due to the potential costs of tax credits (Crompton 2001). However the Act was passed at the final hour. The Act, upon FDA approval of an orphan drug designation, allows a tax credit of up to 50% of clinical trials with assistance in protocol design (especially useful to SMEs), government grants and contracts for clinical trials and an exclusive marketing right of seven years from the date of FDA marketing approval. These incentives were intended to encourage innovation and are particularly attractive in chronic disease R&D, as drug provision will be long-term providing a steady income stream.

Concerns have been raised about abuse of the system and that private industry has profited by public research, thereby making the public pay twice – once for the research and again for what is perceived to be an overpriced product. Changes in policy and many debates about possible changes to the OD Act have created uncertainty in the industry as to whether, after perhaps years of development, the rules may change. This uncertainty may retard development:

> 'It is ironic that the very process of looking for a way to curb abuses in a statute designed to foster innovation, could deter that innovation.' (Rhode, 2000, p.138).

5. The EU Orphan Drug Regulation (2000)

The US Orphan Drug Act (1983) with its incentives, both financial and regulatory, has led to 837 medicinal products being awarded orphan drug status. At the end of 1997, 152 orphan products had obtained marketing approval. These products are now being used by over eight million patients (Reider, 2000). The 1983 Act is widely regarded as one of the most successful pieces of health-related legislation enacted so far in the USA, fostering the creation and growth of many small to medium sized biotechnology companies. These successes could potentially be repeated in the UK under the European Orphan Drug Regulation which became fully operational in May 2000 under pressure from the EU Parliament (Torrent-Farnell, 2001). The regulation provides incentives for drug manufacturers to invest in orphan drug R&D. Regulation 847/2000 stipulates the rules under which orphan drug status may be given in order to receive these incentives. Compliance to these rules requires detailed documentation and solid scientific evidence, ergo non-contradictory to known scientific understanding. For example applicants have to prove a product is:

> ' Intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5:10,000 persons.'

Further proof is required that, without the Orphan Drug incentives, a product would be unlikely to generate sufficient returns to justify R&D and marketing investments. A comparison of the OD legislations of the EU, US, Japan and Australia are shown in Box 2 below.

Box 2

National Orphan Drug Regulations

	EU	US	Japan	Australia?
Year	2000	1983	1993	1998
Prevalence per 10,000	<5	<7.5	<4.2	<1.1
Protocol assistance	80% reduction	Yes	Yes	No
Fees waiver	50% reduction	Yes	c35% reduction	Yes
Market exclusivity	10*	7	10	?
Research grant	No**	Yes-FDA	Max 50% p.a.#	No
Tax credit	Up to member state	50%	% decided by KIKO	No

** This may be reduced to 6 years if OD criteria is no longer met, or OD becomes excessively profitable.*

*** There are no grants available from EMEA or COMP but economic help is available from Member states or EU institutions (e.g. VIth Framework Programme).*

 # This is subject to part repayment if sales reach more than 100m Yen.

? Australia is presently reviewing its OD procedures so these may change – results expected July 2002.

Source: Adapted from Management Forum (2001)

The costs of developing medicinal products for the treatment of rare (orphan) diseases are disproportionately high in relation to the volume of products likely to be sold, since there are few sufferers needing treatment. However the costs of developing drugs is disputed (see Box 3 below). The R&D strategies of the large UK pharmaceutical companies appear to be driven by the 'big hits' (such as cancer and heart disease) and do not include orphan drug or rare disease

research, due to a perceived lack of potential profit (Crompton 2001). Some research is already funded by member states, through public research laboratories and academic institutions, complemented by charities.

> 'The challenge of rare diseases is great because it's an area that few actors have paid attention to, either from a discovery point of view or development process'
>
> Andrea Rappagliosi: VP Health Policy and Government Relations, Serono International (2000) EPPOSI (2000).

However this funding is not enough to pay for the clinical trials, manufacturing, patent, marketing and regulatory costs necessary to make therapies available for rare diseases. It normally requires the resources of the pharmaceutical and biotechnology industry, with the added backing of venture capitalists (in some cases) to take promising projects forward. There was a firm commitment by the European Commission that patients suffering from rare diseases should be entitled to the same quality (of safety and efficacy) as other patients in the EU, hence the high scientific and ethical standards of the Regulation. Patient representation, in a new patient driven approach, was deemed paramount and patient representatives were included in a continuous dialogue with all other interested parties. One of the aims of the regulation was to boost research, development and innovation in novel drug developments, with particular attention to emerging biotechnology derived products (Torrent-Farnell, 2001).

6. Committee on Orphan Medicinal Products (COMP)

COMP was formed by EMEA (European Medicines Evaluation Agency) in April 2000. COMP's remit is to examine all applications for Orphan Medicinal Product (OMP) designation submitted in accordance with Regulation (EC) 141/2000. COMP is comprised of 1 representative from each member state, 3 from EMEA and 3 from patient organisations (total of 21 members. COMP advises the European Commission on the establishment and development of ODP policy and assists the Commission in drawing up detailed guidelines and liaising, at both the European level and internationally with the pharmaceutical industry, academia, learned societies, patient organisations and institutional

bodies on matters relating to OMPs (www.emea.eu.int). COMP, whilst doing scientific assessments does not perform the assessment on the quality, safety and efficacy of OMPs.

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7. The disputed costs of research

Support for orphan drug incentives are not universal. One staunch opponent who has lobbied the US Senate about what he sees as government sponsored monopolisation argues:

> 'The Orphan Drug Act is used to privatise something that is in the public domain, such as an invention paid for by tax dollars, or a patent that has expired. It is particularly important to a company when they have done the least to deserve the benefit. Companies use the Orphan Drug Act to stop other companies from investing in clinical research, or from bringing new innovative products to market… Companies that obtain Orphan drug designations in the United States use the exclusivity provisions to build a wall around an invention in the public domain, by obtaining patents on various manufacturing methods, treatment regimes or minor improvements in the product, in order to create barriers against entry by competitors'.
>
> Love (1999 www.cptech.org)

Love further claims, as examples:

> ' Amgen used its Orphan Drug status to build a wall of manufacturing patents around EPO, which was in the public domain, and Bristol-Myers Squibb used Orphan status to keep a competitor from submitting its own clinical research on the use of Palliate for Karposi's sarcoma'

Public Citizen is a Washington based non-profit lobbying organisation with15,000 members, representing consumer interests. Congress Watch, which is one of its five divisions, produced a report Rx R&D Myths: The Case Against The Drug Industry's R&D ''Scare Card'' (July 2001 www.citizen.org 14.11.01), which launches a scathing attack on the pharmaceutical industry's

claim that it needs extraordinary profits to fund expensive, risky and innovative R&D and that any legislation that might lower prices or profits would harm millions of Americans.

> 'But this R&D scarecard – or canard – is built on myths, falsehoods and misunderstandings, all of which are made possible by the drug industry's staunch refusal to open its R&D records to congressional investigators or other independent auditors.' Public Citizen (2001)

Their findings based on government studies, company filings with the US Securities and Exchange Commission and documents obtained via the Freedom of Information Act are reproduced here in full, due to their specific claims (backed by evidence, which can be followed up by the reader via the given website) in Box 4.

Box 4: Signs of Abuse?

- ? The drug industry's claim that R&D costs total $500m for each new drug (including failures) is highly misleading. Extrapolated from an often misunderstood 1991 study by economist Joseph DiMasi, the $500m figure includes significant expenses that are tax deductible and unrealistic scenarios of risks.
- ? The actual after-tax outlay – or what drug companies really spend on R&D – for each new drug (including failures) according to the DiMasi is approximately $110m (That's in year 2000 dollars, based on data provided by drug companies
- ? A simpler measure – also derived from data provided by the industry- suggests that after-tax R&D costs ranged from $57 to $71m for the average new drug brought to market in the 1990s, including failures.
- ? Industry R&D risks and costs are often significantly reduced by taxpayer-funded research which ahs helped launch the most medically important drugs in recent years and many of the best-selling drugs, including all of the top five sellers in one recent year surveyed (1995).

- An internal National Institute of Health (NIH) document, obtained by Public Citizen through the Freedom of Information Act, shows how crucial taxpayer- funded research is to top-selling drugs. According to the NIH, taxpayer-funded scientists conducted 55% of the research projects that led to the discovery and development of the top five selling drugs in 1995.
- The Industry fought and won, a nine-year legal battle to keep congressional investigators from the General Accounting Office from seeing the industry's complete R&D records. Congress can subpoena the records but has refused to do so. That might owe to the fact that in 1999-2000 the drug industry spent $262m on federal lobbying, campaign contributions and ads for candidates thinly disguised as 'issue' ads.**
- Drug industry R&D does not appear to be as risky as companies claim. In every year since 1982 the drug industry has been the most profitable in the United States, according to *Fortune* magazine's rankings. During this time, the drug industry's returns on revenue (profit as a percent of sales) have averaged about three times the average for all other industries represented in the Fortune 500. It defies logic that R&D investments are highly risky if the industry is consistently so profitable and returns from investments are so high.
- Drug industry R&D is made less risky by the fact that only about 22% of the new drugs brought to market in the last two decades were innovative drugs that represented important therapeutic gains over existing drugs. Most were 'me-too' drugs', which often replicate existing successful drugs.
- In addition to receiving research subsidies, the drug industry is lightly taxed, thanks to tax credits. The drug industry's effective tax rate is about 40% less than the average for all other industries.
- Drug companies also receive a huge financial incentive for testing the effects of drugs on children. This incentive called paediatric exclusivity, which Congress may re-authorise this year, amounts to $600m *in additional profits* per year for the drug industry – and that's

just to get companies to test the safety of several hundred drugs for children. It is estimated that the cost of such tests is less than $100m per year.

? The drug industry's top priority increasingly is advertising and marketing, more than R&D. Increases in drug industry advertising budgets have averaged almost 40% a year since the government relaxed rules on direct-to-consumer advertising in 1997. Moreover, the Fortune 500 drug companies dedicated 30% of their revenues to marketing and administration in the year 2000, and just 12% to R&D. *****

Further support, with references, is given by The Project on Government Oversight (POGO) at www.pogo.org/drugs/health.htm (11.12.01). POGO state that the pharmaceutical industry's contribution to political candidates in 1997-98 was $9.7m and the industry spent $74.4m on hired lobbyists. Spending on advertising in 1997 was $1b. POGO also report that pharmaceutical companies are delaying the production of generic drugs by *'filing frivolous lawsuits for the sole purpose of delaying the expiration of patents'*

8. Intellectual Property Rights – Patents, Market Exclusivity for Orphan Drugs

Raw DNA (information) is not allowed to be patented as genes are not 'man-made', however when whole genes, which are complex organic molecules, are isolated and purified from the chromosome where they reside they are eligible to be patented as chemical compounds. A genetically engineered bacterium was first patented in the US in 1980. Meanwhile the European Patent Office (EPO) did not extend the scope of patentable subject matter from plants (1989) to animals until 1992 (the Harvard 'oncomouse'):

> 'This [delay] sparked years of litigation which contributed to significant uncertainty as to the level of protection provided by the EPO' [regarding gene patents] 'While Europe debated, the US innovated, producing such companies as Celera, Incyte and Amgen'

Corwin & Lesko (2000)

Larger US pharmaceutical companies were stimulated to pursue active genomic businesses. However Monsanto did not fare well in its marketing of genetically modified crops. Also whilst the US viewed innovation as an opportunity to compete globally, 'to grow their nation', the UK government 'was tempted to hide behind their version of regulation in order to do nothing' (The Public Health Genetics Unit 1999).

Pharmaceutical medicines are not considered as ordinary goods (World Intellectual Property Organisation [WIPO] 2001). The consumers cannot evaluate the quality, efficacy and safety of the drugs and because they play a significant social role in realisation of the fundamental right (as accorded by the WHO) to health. This is similar to the argument that health care is unique and should be approached differently from other social goods.

A patent confers its owner a time limited monopoly right to operate in a defined technical area. Disclosure of patents promotes technological exchange and eventual copying into generic products. Patents are usually applied for early in the research stage to protect against competitors. Although eligibility for OD status can be attained at any stage of development. exclusivity under the OD regulation applies upon market approval by the European Medicines Evaluation Agency (EMEA).

> 'Patents and orphan drug protections provide complementary protection for biomedical research and clinical development. Given time and provided that member states develop sensible drug pricing structures, this research will yield access to therapies for patients'
>
> Cozens, P. (Propharma Partners Ltd) EPPOSI (2000)

IPR policies need to respond rapidly to innovations in biotechnology, in order to exploit their economic worth and to encourage innovation for the good of society as a whole. There appears to be a problem in how to protect innovators, through IPR, to encourage technological development, without creating monopoly rights to powerful companies who may use the system to patent 'inventions' which are far from original or inventive, stifling creative innovation by small players. IP is central to economic success and companies are developing IP strategies with the goal of creating barriers to competitors, whilst using technology such as corporate intelligence tools to exploit the

strengths and weaknesses of competitors. (Intellectual Property Worldwide 1999). IPR is becoming a strategic weapon for prosperous companies, using the complexity of IPR legislations against competitors by creating time delays, market uncertainties and huge legal costs, thereby causing the strangulation of innovation. An example of such strategy can be seen in a high technology precedent - Nintendo's anti-trust and copyright litigation mentality led to the industry joke that Nintendo was in: 'two businesses, video-games and litigation' (see www.prcentral.com). In biotechnology Thompson (2001) claims *'everybodys suing everybody else to grab rights to potentially lucrative genes'*, giving the examples of Elan v The Mayo Clinic, The University of Rochester v Pharmacia, Amgen v Transkaryotic Therapies, who have all clashed over patent disputes. The fear of ineffective or unfair IPR protection, especially in SMEs may deter Mode 2 knowledge producers from participation, thus hindering technological and economic progress. With the pressure on government funding for R&D private industry will need new incentives to increase their R&D and therefore need the assurance of IP protection in whichever medium they use to create knowledge else they will rely on secrecy. Secrecy threatens the expansion of knowledge and leads to the duplication of expensive research by others.

Will patents on genetic material be to the publics' benefit or will pharmaceutical companies use them to stifle competition and innovative, potentially life saving scientific advances? A balance between encouraging innovation and the availability of generic medicines is important. A strong generic sector is a powerful stimulus to innovation and a necessary component of cost-containment for the health care systems of member states.

Genewatch U.K. accuse companies of using patents to stifle research and charging monopolistic prices thereby jeopardising healthcare and innovation. Genewatch (2001) give the case of Myriad Genetics Inc. who, between 1998-2000, were awarded nine US patents on the breast / ovarian cancer genes BRCA1 and BRCA2. These gave Myriad the exclusive right to commercialise laboratory-testing services, diagnostic test kits and therapeutic products, which use these two gene sequences. Myriad defends its' patents rigorously and legislatively and is accused by US researchers and laboratories of stifling

research and restricting women's access to DNA testing. It is claimed that BRCA1's discovery was based on international collaboration and the open exchange of information between disparate academic (public funded) researchers and laboratories. Patients themselves donated tissue and researched their family histories to provide clues. BRCA2s discovery is also claimed to follow groundbreaking work at Britain's charity-funded Sanger Centre and the Institute of Cancer Research (ICR). The Myriad BRCA1 gene was given an EPO patent on 10.1.01, allowing Myriad to profit. This patent is being opposed by the Institute Curie in France with the support of other organisations, for its overly broad claims and the threat that a Myriad monopoly would jeopardise research and hinder access to testing www.curie.net/actualities/myriad/declaration_e.htm (1.11.01). Myriad insists that tests are done through Myriad's laboratory in the US (at almost three times the cost in France). The grounds for opposition are – lack of novelty, lack of inventive step and insufficient description. Another example given (see Box 5) is that of Amgen which patented DNA sequences encoding erythropoietin for a product called Epogen (EPO) in October 1987. The identification of the EPO protein in 1977 resulted from two decades of US government funded research. Amgen however won, through protracted litigation, the race to exclusive rights to manufacture its recombinant version of EPO (Epogen), which was the most expensive drug in the US Medicare scheme. In 1999 US sales of Epogen were worth c$1.8b

Box 5: Amgen and Epogen

Whilst its first EPO patents were process patents on isolating and cloning the gene, Amgen took out product patents in the 1990s which claim that it owns the rights to all artificial EPO made from mammalian cells. As a result, the company sued Transkaryotic Therapies (TKT) and Aventis on the grounds that they had infringed its patents by developing a technology to activate the EPO gene in human cells. Even though TKT only used regulatory sequences to activate EPO genes that were already present in the cells – and so consciously avoided the use of any of Amgens technologies _ Amgen won this crucial battle on 19th January 2001 with far reaching implications for future drug

development. If this decision is upheld on appeal Amgen's strategic timing of its patent applications (the first was granted in 1987 while the last will expire in 2015) will extend its monopoly on Epogen to nearly 30 years, inflating drug costs and stifling competition for much longer than the 17 years for which patents are normally granted. (Reuters 22.1.01, quoted in Genewatch UK)

Source: Genewatch UK (2001)

Bioethics Professor Jon Merz claims that twice when he surveyed laboratory researchers around 25% reported that they had abandoned research because of established gene patents. Patents are believed to increase costs of academic research, thereby stifling new discoveries.

> 'Patent attorneys regularly advise researchers to restrict their presentations to colleagues, don't show your work, don't show your notebook, don't give that talk, so as not to jeopardise the planned patent submissions. This has reversed the half-century culture of free and open communication in the scientific communities' (King 2001).

In 2000 a groundbreaking lawsuit was brought by parents of children suffering from Canavan disease (a rare progressive fatal disorder), against researchers at Miami Children's Hospital who had patented a pre-natal test. The patent holders also tried to restrict the number of laboratories and the number of tests in order, it is alleged, to enable the hospital to issue an exclusive licence for the test and receive patent royalties. However the parents accuse the hospital of profiting from the children's illness and hindering access to tests and future research. The researchers had been given, freely and for the public good, tissue from one family's two dead children in 1981 for the Canavan project. The hospital patent even made free genetic screening too expensive to offer by rare disorder charities.

> 'The suit does not directly challenge the patent but alleges that the researchers secretly obtained it using the genetic information and financial resources that had been donated for the public good and

began charging royalties and limiting the availability of testing.' DeFrancesco (Editor Bioreseach Online) 2000.

So are these isolated incidents that have arisen through greed, or anomalies in the patenting laws?

9. Barriers to Orphan Drug development and availability

As the EU Regulation is still in its infancy there may be teething problems, or unexpected or new problems may arise based on:

- Exaggerated expectations fuelled by media hype or industry propaganda
- Ungrounded fears about biotechnology: for example GM food.
- Ethical objections: for example to the use of embryonic material.
- Historically based fears of eugenics
- Deficits in genetic services, diagnosis is a lottery (Crompton 2001)
- A lack of multidisciplinary collaboration, between scientists themselves and science and industry, politicians, regulatory bodies etc. (Non 'joined up' administrative departments). For example Francoise Grossetete (Member of the European Parliament at EPPOSI 2000) raised concerns that EU member states had not taken any action to create a common research centre, instead preferring to encourage competition and rivalry. She urged members to join forces to overcome this medical obstacle.
- A lack of, or decreasing funding for basic research to feed into industrial innovation.
- Common drugs are tested on thousands of human patients to assess safety. In an orphan, geographically dispersed, population clinical trials may only be done on as few as one to four patients. Although the treatment may be better than nothing the side effects, which may be disastrous, may not be known. There is also concern about increased insurance costs and product liability claims, even though it is felt that courts will be sympathetic to industry. However the possibility of huge damages claims may discourage innovation in the OD market, especially for small firms. According to Buckingham (2001) after the

atrocity of September 11th, a tougher line has been taken by insurance underwriters, resulting in premiums having increased by 400% and liability cover reduced by 25%. Some sections of the pharmaceuticals sector may no longer be able to buy insurance cover at all in the commercial market. There are concerns also, from the insurance industry, about the quality of clinical trials, which have resulted in product recalls and claims for compensation from consumers. There is support for these concerns' For example the Report of the Science Advisory Board, Committee on the Drug Review Process Appendix C-2 (December 3, 1999) gives as one of four general observations:

'One is that the UK system of clinical trials of new products is controversial. A ten- year audit of such trials found that the procedures to decide the safety and effectiveness of new products were flawed to the point of endangering the health of those taking part. In a sample of 226 trials, significant under-reporting of side effects was found in about 30%. Insufficient proof of drugs being stored at the correct temperature was found in 55%, and 43% of patients were found not to have been given clear instructions about the use of the drug being tested. There have also been reports that international manufacturers have taken to testing their products in the UK in recent years because the trials they want would not be permitted in other jurisdictions, notably the United States. These allegations are of course contested'.

? The American FDA is reported, by Buckingham (2001), to be giving fast track approvals in situations where it would not have done so twenty years ago. Pressure from consumers for new drugs also means that companies cannot carry out the extended trials they may have previously done. According to Buckingham (2001) insurers say life saving drugs may not be withheld from the public but admit that some 'marginal treatments might not go into production. This may have severe repercussions for orphan drugs

? Market fragmentation. Different health care systems in member states, which slows the uptake of innovative new medicines. There are different assessment criteria on cost-effectiveness which may make a drug cost-effective in one member state and not another due to price

differentials. There can be as much as 4 years between the first patient in one member state having access to an innovative new medicine and access to it being available to a fellow patient in another member state (EC, EDG 2000).

? A lack of overall incentives for small to medium size (SME) companies.

? The fear that broad gene patents may damage an environment of innovation.

? Inadequate commitment from member states to follow EU legislation.

? The National Institute for Clinical Excellence:- Beta Interferon is perceived to be of benefit to a sub-set of Multiple Sclerosis (MS) patients. The issue of Beta Interferon's use for the treatment of these 'relapsing / remitting' (MS) patients was raised on 3.4.01 by Baroness Cumberlege, in the House of Lords (Lords Hansard text 210403-20). Beta Interferon was referred to NICE for approval on 6.8.99 and the results were not expected until November 2001. The desperate wait for this medicine extending to 27 months.Lord Clement Jones, n the same debate, argued that the incidence of relapsing remitting MS is 3.8:10,000 of the general population so Interferon may be claimed to be the first OD assessed by NICE. There is a concern over the appropriateness of cost economic evaluation and this case raises fundamental questions about NICE's future recommendations regarding the supply of treatments for rare diseases under the NHS. The development and production of OD faces a fourth hurdle after safety, quality and efficacy, as recognised by the pharmaceutical industry who see the UK as erecting barriers to innovation. It is not appropriate to use standard cost-effectiveness criteria in the assessment of a drug for a rare disease. The increase in health spending in the NHS (4.7% above inflation for three years) has to be spread between the reform programme under the White Paper 'The New NHS. Modern and Dependable' and liabilities under minimum pay legislation and the maximum working hours directive. There will be few additional

resources available for opportunities presented by genetic advances (Ling 2000).

References

Buckingham, L. (2001) 'Insurers Put Pressure on Drugs Firms,' *Financial Mail on Sunday* (2.12.01, p11)

Burrell, G. and Morgan, G. (1979) *Sociological Paradigms and Organisational Analysis* (p1-7). London:Heinemann.

Cohen, W.M. and Levinthal, D.A.(1990) Absorptive Capacity: A New Perspective on Learning and Innovation, *Administrative Science Quarterly* 35.

Collyer, F. (1996) Frankenstein Meets the Invisible Man: Science, Medicine and a Theory of Innovation, *Electronic Journal of Sociology* www.sociology.org/content/vol002.002/collyer.html (14.10.00).

Corwin, D.S. and Lesko, P.A. (2000) Debunking the Uncertainty Surrounding Genome Realted Patents, *IP Worldwide: The Magazine of International Law and Policy for High Technology* Aug/Sept 2000.

Crompton, H (2001) *Rett Syndrome, Rare Diseases and UK Research*, Manchester Metropolitan University Business School Working Paper Series WP01/14 July 2001.

DeFrancesco, L. (2000) Gene Patenting Run Amok? www.bioresearchonline.com 1.11.01

European Platform for Patients Organisations, Science & Industry - EPPOSI (2000) Report of the First EPPOSI Workshop on Rare Disease Therapy Development and Partnering, Brussels 21st September 2000.

Erno-Kjolhede, E. (2000) *Scientific Norms as (Dis)integrators of Scientists?,* MPP Working Paper, No.14/2000 (October 2000) ISBN 87-90403-82-7.

Genewatch UK. (April 2001) Patenting Genes – Stifling Research and Jeopardising Healthcare, www.genewatch.org (31.10.01).

Gibbons. M., Limoges, C., Nowotny, H., Schwartzman., Scott, P. and Trow, M.. (1994) *The New Production of Knowledge:The Dynamics of Science and Research in Contempory Societies*, London: Sage

Hawkes, N. (2001) New MS Drugs 'Should Not be Given on NHS', *The Times* (3.11.01).

Idris, K. (Director General WIPO) Message from Dr. Kamil Idris www.wipo.org/eng/dg_idris.htm (30.6.99).

Intellectual Property Worldwide, March/April 1999 p.20-35, American Lawyer Media Inc.

Knorr Cetina, K. (1995) *'Laboratory Studies: The Cultural approach to the Study of Science'* in Jasanoff, S., Markle, GE., Petersen, JC. and Pinch, T. (Eds), Handbook of Science and Technology Studies, London: The Society for Social Studies of Science.

Love, J. (1999) Health Care and IP: The Orphan Drug Act, www.intelliwareint.com/gls-cdrom/CPT/DrugAct.htm 30.11.01

Matusik. K.F. and Hill, C.F.L. (1998) The Utilisation of Contingent Work, Knowledge Creation and Competitive Advantage, *Academy of Management Review* (1998) Vol.23 No.4 p680-697.

Nonaka, I. and Takeuchi, H. (1995) *The Knowledge Creating Company*, Oxford: Oxford University Press.

Norus, J. (1998) The Role of Small Entrepreneurs in the Biotechnology Industry www.sbaer.uca.edu/Research/1998/ICSB/r001.htm (24. 9. 01)

Ohmae, K. (1990) *The Borderless World: Management Lessons in the New Logic of the Global Marketplace,* New York

Oliver, R.W. (1999) *The Coming Biotech Age: The Business of Bio-Materials,* New York: McGraw-Hill.

Powell, W.W., Koput, K.W. and Smith-Doerr, L. (1996) Interorganisational Collaboration and the Locus of Innovation: Networks of Learning in Biotechnology, *Administrative Science Quarterly,* 41 , 116-145.

Powell, W.W. (1998) Learning From Collaboration: Knowledge and Networks in the Biotechnology and Pharmaceutical Industries, *California Management Review* Vol.40, No 3, Spring 1998.

Reider, C.R. (2000). The Orphan Drug Act: Provisions and Considerations, *Drug Information Journal,* Vol.34, p.295-300.

Rhode, D.D. (2000) *Food and Drug Law Journal,* Vol. 55, p125-143.

Rifkin, J. (1998) *The Biotech Century: Harnessing the Gene and Remaking the World,* Jeremy P. Tarcher / Putnam.

Senker, J et al. (1999) Literature Review for European Biotechnology Innovation Systems (EBIS), EC TSER Project (SOE1-CT98-11117)

The Public Health Genetics Unit (PHGU). (1999) The Nuffield Trust Genetics Scenario Project: Notes of the Workshop for the Pharmaceutical Industry 14.

Thompson, N. (2001) Gene Blues *The Washington Monthly* April 2000

Thurow, L.C. (1997) Needed: A New System of Intellectual Property Rights, *Harvard Business Review*, Sept/Oct 1997.

Torrent-Farnell, J. (2001) Notes at The Management Forum seminar on Orphan Drug Designation: Current Status in the EU on 19th November 2001 London

Uhlin, A, Ragnes, J.and Synnovag, M.C. (2000) The Third Triple Helix Conference – The Endless transition: Modelling and Facilitating Prospective Innovation Systems www.program.forkningsradet.no/bro/hm/body_rio_paper.html 7.11.00

Webster, A (1991) Science, Technology and Society: New Directions, p110-115, MacMillan

Winner, L. (1977) *Autonomous Technology: Technics- Out- of -Control as a Theme in Political Thought*, Cambridge, Mass: MIT Press

World Intellectual Property Organisation (May 2001, WIPO/ECTK/SOF/01/2.5) International Conference on Intellectual Property *The Internet, Electronic Commerce and Traditional Knowledge: Recent Developments and Challenges in the Protection of Intellectual Property Rights, Pharmaceuticals and Biotechnological Inventions.*

Ziman, J. (1994) *Prometheus Bound: Science in a Dynamic Steady State*, Cambridge: Cambridge University Press.