

Whatever happened to the Norwegian Medical Need Clause? Lessons for current debates in EU pharmaceutical regulation.

## 1. Introduction

The growing pressure on Europe's health systems permeates every aspect of contemporary European Union (EU) health policy as governments, insurers, regulators and industries fight to balance sustainability and cost-efficiency with the provision of high quality healthcare (for an overview of contemporary challenges see EPHA 2013; Karanikolos et al. 2013). One area increasingly targeted is prescription drug usage and costs and a range of national and European level policies have been developed and debated which attempt to improve cost-efficiency in pharmaceutical spending by increasing the quality of the drugs being brought onto the market and linking this to pricing. For instance, the recent German reforms, introduced in 2011, require drugs to be priced in accordance with their performance against other treatments; similar debates about the appropriate relationship between price and 'added value' have since emerged in the United Kingdom (UK) (Buko Pharma 2013; Pharma Times 2013). In 2014, the French Court of Auditors published a report advocating the promotion of generics and rational drug use as a tool for curbing expenditure, whilst most recently, the European Parliament has commissioned a study of harmonised assessment of added therapeutic value (ATV) in relation to innovation and pricing (EurActiv 2014; European Parliament 2014).

What these policies have in common is an objective to reduce expenditure on pharmaceuticals by linking the price of drugs to their 'added value' (greatest efficacy at the lowest cost) and, if indirectly, limiting the number of available drugs. However, they also hold the potential to improve health by increasing the clinical value of drugs and encouraging rational use, to reduce illness by limiting exposure to unsafe medicines and unnecessary clinical trials, and to redirect the innovation activities of the pharmaceutical industry. As such, they share objectives similar to a little-known provision which existed in Norwegian pharmaceutical law prior to 1994. The Medical Need Clause ('behovsparagraf' MNC) offers interesting and valuable insights into the challenges currently facing health policy in Europe.

At the twentieth anniversary of the MNC's removal, this article reviews Norway's experience with its MNC and discusses the relevance of a MNC-style regulation for improving health, reducing illness, ensuring sustainable health systems and fostering pharmaceutical innovation. It concludes by asking how these findings can inform current EU debates over the growing cost of prescription drugs and the direction of pharmaceutical development.

## 2. Methodology

A comprehensive review of the existing literature, identification of experts and examination of the prevailing regulatory framework was aided by the reality that the Norwegian pharmaceutical market is '...small and relatively transparent, and the pool of appropriate key persons and relevant literature is modest' (Håkonsen et al. 2009: 284). Semi-structured in-person, telephone and Skype interviews were conducted with nine experts between April and May 2014. These built upon a previous round of seven telephone interviews, some of which were with the same people, which were conducted between November 2013 and January 2014 as part of a related project.

Those interviewed included four representatives from *Statens Legemiddelverk* (Norwegian Medicines Agency NoMA), two from the RELIS Medicines Information & Pharmacovigilance Centre at University of Oslo Hospital, one from the European Medicines Agency (EMA), one from the World Health Organisation (WHO) and one from one of Norway's three pharmaceutical wholesalers. Other

interviewees included a Professor in the clinical aspects of the field at the University of Tromsø, a Professor in the regulatory aspects of the field at the University of Oslo and two representatives from national and international drug bulletins. Individuals from NGOs working on the issue of rational drug use and pharmacovigilance were also interviewed. As is the nature of the Norwegian system, the reason for selection of each of these individuals often lay in their previous or additional experience – expertise contained within the group interviewed includes that gained in relevant positions at the WHO, the EMA, the Norwegian Board of Health, the National Insurance Agency, the Open Society Foundation, the Pharmacopeia International Advisory Committee and the research divisions of at least two multinational pharmaceutical companies. Furthermore, at least eight of those interviewed have worked for or with NoMA at some point in their careers. Interviewees' responses are cited and identified in the text according to the following groupings: NoMA; pharmaceutical wholesaler (PW); higher education institution, university hospital or non-governmental organisation (HEI/NGO); drug bulletin (DB); and EMA or WHO (EMA/WHO).

A broad literature review was also conducted, encompassing English and Norwegian language research. The pool of relevant key literature on the Norwegian pharmaceutical market is modest – that relating specifically to the implementation and impact of the MNC is even smaller. An initial keyword search was supplemented by literature recommended by interviewees and relevant sources within this cross section followed up. The collection was abstracted by one author and discussed between both, being used to inform interviews and as a comparator for data gathered. The literature is primarily comprised of academic studies but also includes national- and EU-level legislation, government documents, news reports and research conducted by NGOs.

### 3. The Norwegian case

Norway was one of the first countries to have a system for the regulation of pharmaceutical products, dating back to 1928 (Dukes 1986). Originally requiring demonstration of quality, safety, efficacy and cost, the authorisation process was amended 10 years later to state that 'there should be a clear-cut medical need for any new product' and 'new drugs should represent better therapeutic alternatives than those already on the market' (Jøldal 1986: 664). An official definition of 'medical need' was never documented – instead, it was for the registration board to establish its own practices, which remained unpublished and unknown to the outside world (Andersson 1992; Interview HEI/NGO). Moreover, according to Andrew et al. (1995: 31), 'emphasis on particular criteria has varied over the years. In the 1950s the focus was on quality, in the 1960s on safety and in the 1970s on efficacy. During the 1980s the economic aspects...received greater attention'. In general, as was made clear in our interviews, the MNC enabled the Norwegian government to maintain tight but evolving control over the prescription drug market. One interviewee described the MNC model as a 'dictatorship', where government decisions were made behind closed doors with little openness or input from the pharmaceutical industry or wider public stakeholders (Interview HEI/NGO). The Director of Health could act upon advice without transparency, thus avoiding the political struggles and industry lobbying inherent in much of pharmaceutical policy-making.

The flexible Norwegian system allowed the regulatory body to restrict the number of drugs on the market to '...what was stipulated as the minimum required to achieve a rational and effective use' (Håkonsen et al. 2009: 278). This policy saw drugs already licenced in Britain, France and Germany, as well as other Nordic countries, rejected in Norway (Smith 1985). In the 1970s, the general trend was to make between five and seven different brands of the same substance available and the net effect was to limit the number of drugs on the market to around 2,000 (Andersson 1992; Lu et al. 2011). As Andrew et al. noted in 1995, the policy '[has] kept the number of drugs marketed at a low

level for the past 25 years, with around 2,200 products... This compares with non-Nordic European countries where numbers range between 7,000 and 25,000' (1995: 46). The number of generics on the market was low, since these were 'usually regarded as not needed, unless they offered price advantages' (Norris 1998: 70). Between 1981 and 1983, approximately 40 per cent of market authorisation applications were rejected and the MNC was involved in 60 per cent of those decisions (Jøldal 1986: 665).

Upon receipt of an application, the Specialities Committee of the National Centre for Medicinal Products Control – *Statens Legemiddelkontroll* (SLK) – would undertake five key steps. Firstly, it would assess whether any medical need for the product existed. If not, no further evaluation was carried out; here the MNC served two additional purposes in reducing the workload of the regulatory agency and accelerating the authorisation process for important drugs satisfying an unmet medical need. Though clinical trials were not a prerequisite of the approval process, comparison of the new drug to existing products, and thus clinical trial data in some form, was necessary. Though anticipated cost often influenced the approval process, formal price negotiation – the second step – began only after authorisation was granted and the agreed price could not be 'in disproportion to its value' (Jøldal 1986: 669). Once approved and priced, drugs were added to the inventory of the state-controlled monopoly wholesaler, the *Norsk Medisinaldepot* (Norwegian Medicinal Depot NMD). A third and particularly important element of the MNC was the limited term approval period applied to all drugs, which lasted just five years. In a fourth stage, drugs were subject to re-assessment after this period and, unless a satisfactory level of quality, safety, efficacy and need was demonstrated, were taken off the accept list or granted conditional authorisation, subject to re-assessment.

Crucially, rejection of an application for market authorisation did not completely exclude physicians from accessing the medicine but rather led onto a fifth step. The special licensing procedure, introduced in 1941, allowed physicians to apply for use of drugs not approved by the SLK in special circumstances. The literature notes that whilst 'special justification' was required, in practice very few applications were rejected and the licences were often employed to circumvent regulatory requirements (Hemminki 1981: 1059). In 1977 16,000 special licences were granted (Smith 1985: 532); these accounted for 2.4 per cent of total national drug expenditure in that year, but in some large regional hospitals, could account for as much as 20 per cent of spending on medicines (Hemminki 1981: 1060; Bakke 1986: 254). The high usage of the special licence could suggest that Norway was 'free-riding' on the less stringent marketing conditions of neighbouring countries and that successful operation of the MNC was made possible by the availability of a wider range of medicines outside of the national market.

#### 4. The abolition of the MNC and its implications

In 1992 Norway signed the EEA Agreement and was forced to change several elements of its pharmaceutical legislation so as to comply with the established principles of the common market and the European Free Trade Area (EFTA). This included removal of the MNC – though a similar clause had been considered by the European Community in 1963 it was rejected under heavy industrial pressure (European Commission 1963; Dukes 2005; Orzack et al. 1992). Prevailing European legislation stated that the only criteria to be taken into account during market authorisation were quality, safety and efficacy (EU Directive 65/65/EC Article 4b) and in addition to the MNC, Norway was forced to change existing regulation concerning price controls, parallel importing and privately-owned wholesalers (Norris 1998). An interesting question emerges when considering the fate of the MNC in comparison to other provisions which conflicted with the principles of the common market. The Norwegian government fought hard to exempt the policy on monopoly control on alcohol sales,

for example, yet the MNC clause was sacrificed. Given that it seemed to be functioning well – understood as controlling the size of the drug market, the level of pharmaceutical expenditure and the rate of consumption – why was the MNC not defended with equivalent vigour?

At the broadest level, lack of public interest and limited public debate combined with uncertainty over the outcome and the overwhelming scale of the EEA negotiations saw the MNC buried (Interviews NoMA). Negotiations were very top-down, meaning that wide-scale consultation with stakeholders was not conducted. Healthcare professionals were unaware of the proposed change, having not been involved in the operation of the MNC previously, and thus did not feel compelled to oppose its abolition (Interview HEI/NGO). As one interviewee stated, ‘no one foresaw or understood the likely consequences and these came too gradually for an instant backlash to occur’ (Interview PW). From a political standpoint, ‘in the tsunami of changes, decisions and implications that followed the EEA agreement, the removal of the MNC got swept away so quickly it could not be used by the opposition parties to criticise the Brundtland government’ (Interview HEI/NGO). Perhaps most interestingly, however, interviewees identified a trading situation – the desire to protect the alcohol monopoly and gain concessions in other sectors meant that the government was forced to sacrifice control in less politically important areas, such as prescription drug policy (Interviews HEI/NGO and PW). In the end, it was the corporatist model of opaque but cooperative policy-making on which the MNC was based which became the reason for its undoing – though it enabled the policy to function well at national level it made it politically weak when caught up in the larger changes brought about by European integration.

[Tables and figures – all inserted here]

Though the prevailing literature projected that the removal of the MNC ‘...is likely to result in an increase in the number of products from 2,200 to around 3,000-4,000 within a few years’ and that the ‘...larger number of synonyms will make the daily life of doctors, pharmacists and patients more difficult’, the post-1994 experiences of the Norwegian pharmaceutical market did not quite mirror these expectations (Andrew et al. 1995: 47). As shown in Table 1, whilst the number of applications did initially rise, it soon levelled out and interviewees from NoMA confirm that this was largely due to the postponement of applications in 1993 (Interviews NoMA)<sup>i</sup>. The size of the market has grown fairly steadily, without a significant post-1994 expansion, and similar gradual increases can be seen in expenditure and consumption (Table 1 and Figure 1). Rather than the predicted increase, drug prices declined steadily between 1994 and 2004 and are now low compared to the rest of Europe – some of these trends can be assigned to changes in the regulation of prices, such as the introduction of reference pricing, which also changed after 1994 (Håkonsen et al. 2009: 278; LMI 2012; Norris 1998: 72). Where an anticipated increase can be seen is in the number of synonym compositions (‘me-too’ drugs) and low ‘noteworthy’ drugs approved (Table 2). Indeed, the literature generally concurs that ‘an increasing number of similar drugs on the market, as well as the introduction of new drugs with limited documentation of efficacy [has become] a major challenge for drug committees...and for prescribing doctors’ (Sandnes 1998: 80).

Norway’s experience with the MNC offers valuable insight into the potential uses of drug regulation in the context of contemporary health systems. The sections below discuss the relevance of prescription drug regulation for health, illness, sustainable health systems and an innovative pharmaceutical industry in light of the Norwegian experience.

## 5. The relevance of a MNC for improving health

From a public health perspective, the costs and benefits of a MNC are determined by the possibility to deliver a high standard of care with a restricted list of available medicines. This is dependent upon a sufficient number of available drugs and a sufficient level of clinical value within the treatment options.

The number of drugs on the Norwegian market has clearly grown since the removal of the MNC, if not at the accelerated rate anticipated in some of the literature (Table 1). The public health value of this larger market is disputed amongst health professionals, with some finding a smaller ‘arsenal’ easier to manage – as examined in the following section – and others preferring as wide a choice of medicines as possible (Lexchin 2002; Smith 1985). The argument can also be made that in certain situations, for example when treating an outbreak of an infectious disease, there is public health value in having a range of similar treatments available (Interviews DB and EMA/WHO). Furthermore, there is a risk that a limited drug list reduces the treatment options for patients with unusual combinations of diseases, who might find that the available treatments for their conditions do not interact well or are ineffective. In general, the literature finds that the medical community is supportive of restricted drug lists providing that, as was the case in Norway, procedures exist which allow them to access non-authorised medicines in special circumstances (Bakke 1984; interview EMA/WHO), though the prescribing habits and approaches of individual physicians are key. Jøldal (1985: 69) concludes that ‘Norwegian drug restriction policy has demonstrated over a number of years that it is possible to restrict the number of drugs on the market quite appreciably without any adverse effects on patients’.

A reduction in the number of available drugs might be at least partially offset by increasing the clinical value of the drugs permitted (Norris 1998). Since the MNC was removed, there has been an increase in the number of synonym compositions approved, the number of market applications made and the total size of the drug market (Table 2). When compared to the relative increase in less ‘noteworthy’ drugs approved, this suggests an increase in the type of lower-value drugs which the MNC had sought to restrict (Table 1). Research in 1990 found that Norway received a high proportion of applications for medicines which were found by the US Food and Drug Administration to represent important therapeutic advances, as opposed to those having ‘modest’ or ‘little to no’ advantages over existing treatments, when compared internationally (Andersson 1990, cited in Norris 1998: 70). The MNC encouraged this higher quality of submission by enlisting comparable data and enforcing re-evaluation after five years, removing drugs which failed to demonstrate continued ATV (Jøldal 1986: 666). Indeed, the loss of the five-year licencing limit was identified by interviewees as the most damaging consequence of the EFTA – ‘the problem is that drugs are only updated or superseded – they are not removed...The five year licence limit was the most important part of the MNC’ (Interview HEI/NGO).

The absence of such requirements and the use of placebos for measuring efficacy, rather than testing new drugs against existing treatments, has opened Norway up to a contemporary market where 85 to 90 per cent of new drugs offer little or no clinical benefit over existing treatments (Light and Lexchin 2012). The heavy marketing and over-prescription of low-ATV and ‘me-too’ drugs means that around 80 per cent of medicine expenditures in well-developed health systems such as Canada, are directed to minor variations of existing drugs (Gagnon and Lexchin 2008; Morgan et al. 2005). This problem is further exacerbated by the pharmaceutical industries ongoing attempts to challenge patent law and extract greater profits from existing rather than innovative drugs (See, for instance, Novartis’ case against the Indian government, Ecks 2008; Krishna and Whalen 2013). As discussed in the following sections, this gives a MNC-style regulation the potential to reduce expenditure in a way which is clinically beneficial.

Further public health benefits can be seen in studies which attribute Norway's relatively strong position in the global fight against anti-microbial resistance (AMR), particularly in relation to tuberculosis, to the existence of the MNC in previous years (Dukes 2005; Jøldal 1986). Two interviewees even identified an aversion to over-prescribing of antibiotics as a reason for the original creation of the MNC (Interviews NoMA). A smaller list of drugs means only a limited number of antibiotics are available, reducing the chances of resistance and ensuring a greater number of alternative treatments where resistance does emerge and Norway has been lauded for its success in combatting 'superbugs' that are resistant to antibiotics in other countries (Haug et al. 2010; Mendoza and Mason 2009; Wesenberg 2013).

Though a limited drugs market can easily control the consumption of individual drugs, such as a particular antimicrobial, it has proven less able, in the Norwegian case, to control overall consumption (Table 1). Though consumption has historically been relatively low in Norway – just half the OECD average in 1987 – the data shows a steady increase in consumption during the MNC's operation (Andersson 1992: 25). This is seen both in terms of retail sales, which grew from 3,203m NOK in 1988 to 7,673m NOK in 1997, and in terms of defined daily doses (DDD), which rose from 777m in 1988 to 1,162 in 1997 (Table 1). The abolition of the MNC seems to have had relatively little impact upon this trend, with continuing low growth in pharmaceutical sales and DDD levels which have grown steadily but remain on a par with or below the EU18 average in most drug categories (LMI 2012; OECD 2014). Similarly, consumption of antimicrobials has continued to fall between 2000 and 2010, remaining well below the EU23 average (OECD 2012). As such, drug consumption would seem to be influenced more strongly by population trends relating to ageing and the treatment of chronic diseases, as well as the prescribing habits of physicians (OECD 2014).

## 6. The relevance of a MNC for avoiding illness

In addition to serving public health goals, the literature suggests that a MNC might have relevance for avoiding illness through reduced physician error, moderated drug consumption and a reduction in the number of adverse drug reactions (ADRs).

For health professionals, the MNC limits choice to a more beneficial but smaller range of drugs and thus forms a control on prescribing (Dukes 2005). One of the commonly cited safety advantages of a limited list of drugs is that it reduces the 'arsenal' of which physicians must keep track and maintain working knowledge (Andrew et al. 1995: 47; Jøldal 1985; 1986). As recently as 2013, a number of cases have been reported where doctors have prescribed the wrong drug because, according to NoMA, the plethora of new treatments were easily confused (Bakke 2013: 1). This issue is particularly problematic in psychiatric medicine, where treatment with a 'cocktail' of drugs is common and a larger range of combinations makes side effects harder to predict. In 2012, a 20 year old patient committed suicide – her death was attributed to a reaction to a new combination of drugs (Lund 2013: 1; Øyhovden and Bentzrud 2013: 1).

Where safer prescribing and reduced drug consumption is achieved, a MNC also holds the potential to reduce the incidence of adverse reactions. Statistics from the United States (US) indicate that in addition to over two million serious incidents and 128,000 patient deaths in 2011 alone, mild adverse reactions, of which 81 million are reported per year, can lead to falls, accidents and hospitalisation (Light et al. 2013: 593). The chances of such adverse reactions being experienced are higher in new drugs and in the first 10 years of a medicine's use – the so-called 'inverse benefit law' (Brody and Light 2011; Interview HEI/NGO; Lexchin 2002). Assessing the changing trend in adverse reactions via ADR reporting is difficult because the efficiency of reporting has increased throughout the period

(Interview HEI/NGO) but the five-year approval period and conditional marketing system imposed in Norway reflected the understanding that safety and efficacy can only truly be known after this period of time and some observers note that the country's stringent conditions are to thank for the fact that some drugs – such as benoxaprofen and ticrynafen – which were withdrawn following adverse effects in other countries never made it to the market in Norway (Bakke 1984: 412; 1986: 254; Jøldal 1986: 668).

## 7. The relevance of a MNC for sustainable health systems

The relevance of the MNC in contemporary EU health policy is most closely linked to its potential to moderate pharmaceutical expenditure. The Norwegian clause was based on the philosophy that a smaller number of drugs results in rational use and lower pharmaceutical bills (Norris 1998). Interviewees confirm that, at some point during the MNC's operation, the SLK was requested to reduce expenditure and an unwritten 'economic element' was brought into the MNC (Interviews NoMA). The success of the MNC in controlling pharmaceutical expenditure is widely acknowledged in the literature and Norway's drug spending has historically been relatively low, but the role of the MNC in this trend is challenged by the continued low level of spending which has prevailed since its removal (Figure 1). In 2011 expenditure on drugs was less than half of the OECD average and annual growth in pharmaceutical spending per capita has fallen between 2000 and 2012 (Lu et al. 2011: 17; OECD 2014: 127). Changes to parallel importing and price setting policy, introduced at the same time as the MNC was abolished, have played an arguably more important part in influencing pharmaceutical expenditure (Andrew et al. 1995: 32; Norris 1998: 70).

With the removal of the MNC, the supply of generics has increased. The share of the Norwegian market for generics expanded significantly between 2000 and 2008, following the introduction of the generic substitution law, becoming more stable in recent years – in 2011, generics sales by volume accounted for 41.5 per cent of total sales (Kjoenniksen et al. 2006; LMI 2012: 10). The MNC allowed some synonym products, so as to ensure price competition and security of supply, but this was limited to between two and four drugs and only applied if they offered price advantages (Jøldal 1985: 67; Norris 1998: 70). In Europe, the generics market has faced challenges in light of the new '8+2+1' data and market exclusivity rules, as well as the 15-year patent provision, all of which provide innovator manufacturers with substantially longer periods of protection than previously existed (Adamini et al. 2009). Since Norway observes the outcomes of the centralised European authorisation procedures, some of the post-MNC changes in the generics market may also be attributable to this legislation.

Furthermore, the MNC had a unique effect upon the structure of drug regulation in Norway. During its operation, decisions required little consultation or justification; there was no obligation to treat companies equally when assessing drugs and the administrative process was opaque, giving the SLK considerable leverage in its interactions with drug manufacturers (Norris 1998). The transparency and accountability of the new system requires the SLK to assess all drugs in the same way, regardless of whether or not a synonym product is already on the market. Though understood predominantly as a positive development, interviewees attribute this change in practice to a weakening of the SLK's position, an increase in its workload and a rise in the number of unnecessary drugs on the market (Interviews HEI/NGO and NoMA). Furthermore, an overlooked impact since the abolition of the MNC is the increased exposure of the regulatory system to political pressure – a core example is seen in the case of Ipilimumab, a melanoma drug which was originally rejected by NoMA but eventually permitted following a campaign by patient groups (Interview PW; Wyller 2014). Though the perceived growth of the drug market is not reflected in the data, concerns about the 'health' of Europe's harmonised regulation system and its tendency to privilege industry concerns over public

health raise questions about the value of a less-transparent but stricter-performing regulation such as the MNC (Abraham and Lewis 1999; Interview HEI/NGO).

Such broader sociological points about the value of a MNC are drawn upon in much of the health systems literature. In a sector where regulation is heavily market-based, the MNC is seen as a welcome point for the introduction of social concerns (Norris 1998; Dukes 2005). Such a provision made pre-1994 Norway a pioneering embodiment of the WHO's essential medicines initiative, ensuring that the drug market catered to specific national needs whilst promoting rational use and cost-containment on an equal footing (Jøldal 1986). Whilst the essential medicines approach targeted developing health systems, many of the social aspects of drug regulation which it responded to were and continue to be of importance in European and Western health systems – a review of the field is beyond the scope of this paper but consumer protection, independent regulation, access to medicines, rational use and sustainability are among the key examples (Adamini et al. 2009; Fraser 1985; Garattini and Bertele 2001; Garattini et al. 2008; Lexchin 1990; Medawar 1992; 't Hoen 2002).

#### 8. The relevance of a MNC for fostering pharmaceutical innovation

A final area in which a MNC-style clause might have relevance for contemporary European health systems is pharmaceutical innovation. In recent years, the pharmaceutical sector has been understood to be suffering from an 'innovation crisis', characterised by a decline in the volume of new and innovative drugs being brought to market (Pammolli et al. 2011). However, recent work has sought to dispel this 'myth', noting that production of new medical entities (NMEs) has, in fact, been stable since the late 1960s (Munos 2009). The 'real innovation crisis' is in the production of NMEs with ATV, as demonstrated by greater clinical efficacy than the existing available treatment (Light and Lexchin 2012; La Revue Prescrire 2012). As highlighted by Light and Lexchin (2012; 2015), the current system encourages mostly new drugs with few clinical advantages based on limited evidence that makes it very difficult to know if the drug is vital or not. Kesselheim et al. (2013: 346) concur with this and following a systemic review of the literature argued that, 'overall, we believe that therapeutic value measures hold the greatest promise for evaluating the effectiveness of investments in drug development'. Therefore, as noted in the discussion of public health benefits, a MNC can be framed as incentivising the production of higher value drugs, thus focussing research, the vast majority of which is funded by public or charitable sources, on the development of clinically superior medicines for unmet needs (Interviews EMA/WHO and HEI/NGO; Wemos, 2014). This reflects Munos' conclusion that, in general, 'countries with a more demanding regulatory apparatus... have fostered a more innovative and competitive pharmaceutical industry' (Munos 2009: 964).

In opposition to this, the industry has historically asserted that a MNC-style regulation would be detrimental to pharmaceutical innovation and research. Ahead of proposals to create a restricted list of drugs available on the National Health Service (NHS) in the UK, Smith (1985) used the Norwegian case in a comparison of 'limited list' regimes and concluded that such a system would be disastrous to the British economy. The report described the pharmaceutical industry as 'disenchanted' and 'discouraged' in four case study countries – the 'virtual absence of any pharmaceutical industry' in Australia was examined alongside Canada's success in 'killing its pharmaceutical industry' through restrictive policies (Smith 1985: 533). The absence of innovatory pharmaceutical research departments in Norway led the report to conclude that 'limited lists of the Nordic or Australian type seem incompatible with a research-based pharmaceutical industry'.

A related argument, commonly used by industry to oppose the imposition of stricter regulatory requirements, is that fulfilment of additional criteria slows down the approval process and delays the

bringing of vital new drugs to the market (Dukes 1986). However, evaluations of the Norwegian MNC have repeatedly concluded that no significant time lag for drugs of important therapeutic value was created by the Clause – in fact, the effect was the opposite for this class of drugs, at the expense of slower approval for drugs of lesser therapeutic value (Andersson 1992; Jøldal 1984; Bakke 1984; Norris 1998).

Such reports of strong and active industry disagreement with the MNC were not mirrored in the work of Andrew et al. (1995) which noted general acceptance of the policy amid occasional industry concerns. This discrepancy might be attributed to the unique case of the Norwegian pharmaceutical market, which is small, even in comparison to its Nordic neighbours (Table 3; Jøldal 1985: 68). Its value has increased gradually, following global trends and without notable change in response to the removal of the MNC, but remains low. The manufacturing market is minimal and has never employed many people – though it is a small and relatively safe investment market, in 2012 Norway ranked 20 out of 31 European countries in terms of value of pharmaceutical production (EFPIA 2014; Interview PW). According to *Farmatid* (Norwegian Pharmaceutical Journal) when the MNC was removed the sector went through a period of rapid internationalisation, in line with broader globalisation processes but at present, Norwegian pharmaceutical firms only provide about 10 per cent of the drugs on the Norwegian market (Farmatid 2013). Finally, an interviewee noted the embedded rational prescribing habits of physicians as a disincentive for industry investment – knowing that new products were unlikely to win the trust of an older generation of doctors, industry saw little priority in the, relatively small, Norwegian market (Interview HEI/NGO). As such, Norway has never been a high priority market for multinational pharmaceutical manufacturers (Bakke 1986: 254; Interviews HEI/NGO and PW).

Determining the multi-faceted components which stimulate pharmaceutical innovation is beyond the scope of this article but, concurring with the work discussed at the beginning of this section, there is clear evidence from the Norwegian case to suggest that a MNC-style regulation serves to encourage competition, research and innovation in the pharmaceutical market. Bakke (1984) is a strong proponent of this view, based on the understanding that the Norwegian system put pharmaceutical companies in a stronger position in price negotiations where the drug in question was innovative, and applied the MNC less frequently for NCEs than for new formulations or brands of existing drugs. He also notes that, whilst a restricted drug market may have a restrictive effect upon local-level research, in the Norwegian case the high standard of healthcare and the relatively uniform population pattern made it an ideal area for the conduct of trials (Bakke 1984).

## 9. Conclusion and implications for EU health policy

In theory, the MNC has the potential to reduce pharmaceutical and general health expenditure in a way which is clinically beneficial, without drastically cutting budgets or passing costs on to patients. By limiting approval to drugs which prove added benefit it can contribute to rational use and reduced consumption of medicines, thus better defending against AMR, adverse reactions and inflated drug bills. Furthermore, where innovation is defined as the development of clinically superior drugs, rather than unimproved variations on existing treatments, the MNC can encourage competition and the research of genuinely innovative medicines to address unmet medical needs. In practice, the exposition above shows that removal of the MNC did not bring about the kind of change which might have been expected, largely because mechanisms to address the MNC's objectives were built into other areas. Essentially, the removal of the MNC shifted control from the point of market

authorisation to the point of inclusion in hospital formularies – Norway has thus moved from having an ‘essential drug’ list to a ‘reimbursement’ list (Interviews EMA/WHO; HEI/NGO and NoMA). This is important, since the social and regulatory needs that the MNC existed to address have not gone away. Regulation in the health sector is ‘a continuing process of reacting to developments in the regulated sectors’ – the single European market makes restriction of drug availability more challenging but advances in pharmaceutical technologies and changing demands in the health sector require new and innovative regulatory tools which perform roles similar to those of the MNC (Chinz 2002: 60). Indeed, elements of MNC-style regulation can be seen in many of the solutions posed to contemporary challenges in European drug regulation.

For example, in early 2014 the EU revised the rules which govern the conduct of clinical trials. Though the final text weakened the role of added therapeutic value in the trial process, early drafts of the text contained provisions and amendments that contained elements of MNC- and ATV-related ideas, indicating continued political support for these concepts<sup>ii</sup> (See also Garattini and Bertele 2004: 89). Similarly, EMA provisions for accelerated assessment and conditional marketing authorisation present new forms of necessity evaluation. Traditionally, the EU had restricted itself to activity involving clinical trials and market authorisation provisions, but more recently it has also begun to engage in debates around pricing and reimbursement (Norris 1998: 67; Gorry et al. 2014). It has championed, for instance, the use of HTA. HTA assesses the value of health technologies using a range of economic, clinical and social criteria and in most member states takes some account of the necessity or ‘social value’ of the drug – interviewees commonly cited HTA as a new form of MNC, capable of tying price more closely to ATV.

As pointed out by Mossialos et al. in their seminal work on the European pharmaceutical sector, ‘there are significant limitations to the relevance and transferability of lessons and policies across countries’ (Mossialos et al. 2004: 30). Nevertheless, the sense from the literature and from experts currently working in pharmaceutical regulation is that a formal, dedicated MNC does not need to exist in order for its influence to be felt. Provisions in Sweden and Iceland in the 1980s saw drugs rejected because they were not ‘medically justified’ – the MNC in these countries was not explicit but its goals were nonetheless embodied in the regulatory arrangements (Jøldal 1985: 68; 1984: 82; Bakke 1986: 253). Furthermore, the contemporary developments examined above have shown how elements of the MNC prevail in modern regulatory frameworks, with the same type of indirect impact upon health, illness, innovation and the sustainability of health systems. It can thus be argued that, underlying the continuity and change inherent in pharmaceutical regulation, is the ‘spirit’ of the MNC. Despite its difficult relationship with profit-driven industry interests and opponents of central regulation, the fundamental tenets of the MNC can be found in almost all contemporary pharmaceutical legislation, offering a continually evolving counterbalance to the market-orientated activity of the modern EU health sector.

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<sup>i</sup> ‘In mid-1993 it became clear that the clause would be ineffective from January 1994. As a result, the industry postponed and withheld a number of applications in 1993 – this is reflected in the statistics, a drop can be seen in 1993. In the last month, 173 applications were made (there are usually only 380ish per year) in anticipation of the removal of the clause. Between 1992 and 1994 the total number of applications jumped from 214 to 260.’ (Interviews NoMA).

<sup>ii</sup> The draft report tabled by MEP Glenis Willmott sought to include a consideration of ‘quality of life benefit’ in clinical trials applications, whilst amendments 689, 247 and 288 sought to introduce requirements upon pharmaceutical companies to state the anticipated benefits for trial subjects, therapeutic and public health needs to be satisfied and, most importantly, a provision to only authorise trials which respond to a therapeutic or public health need. See European Parliament (2013).

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