

Pharmaceuticals, the state and the global harmonisation process

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Abstract

This article examines how regulatory agencies' mission to protect and promote public health, enshrined in legislation, has been shaped and limited by commitments to the commercial interests of the pharmaceutical industry. It is argued that the regulatory state has become largely a 'competition state' which considers its primary role to be the maintenance of industry's competitive position in world markets. By examining regulatory developments across the EU, Japan and the US, I shall explain how the competition state became a building block for the global harmonisation process. To legitimise the global harmonisation process in terms of their mission to protect and promote public health, regulators claim that it does not lower safety standards and will accelerate the availability of pharmaceutical innovations to patients who need them. However, evidence is presented to suggest that these legitimising claims are not tenable.

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IN MODERN INDUSTRIALISED COUNTRIES and many more besides, there exist government regulations requiring new prescription drugs to be tested for quality, safety and efficacy by the pharmaceutical industry. Furthermore, government regulatory agencies exist to review the evidence provided by pharmaceutical companies attesting to their drugs' quality, safety and efficacy. In order to be marketed, the quality, safety

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What is known about the topic?

The regulation of medicinal drugs for safety, efficacy and quality by agencies such as Australia's Therapeutic Goods Administration is now framed by a globally standardised system — the International Conference on Harmonisation (ICH) process.

What does this paper add?

Regulatory agencies are part of the contemporary 'competition state' and have adopted the industry ideology of international competitiveness. The case of adverse drug reaction reporting demonstrates that global harmonisation in the case of medicinal drugs is not necessarily consistent with the best interests of public health.

What are the implications for researchers and policymakers?

The highly technical ICH process is dominated by industry and technocrats. There is a need for this process to be subjected to more extensive public and critical scrutiny.

and efficacy of new drugs must be approved by the regulatory agencies concerned. At the forefront of these developments were Norway, Sweden and the United States in the 1920s and 1930s, followed in the late 1960s and 1970s by Australia, Japan, the United Kingdom, Germany and most other Western European countries.

Hence, by the late twentieth century, all governments of developed countries had become legally responsible for the regulation of pharmaceutical products so as to protect and promote public health. However, since the inception of pharmaceutical regulation, its nature has been subject to intense political negotiation and controversy. Broad political discussions about whether there should be more or less regulation of industry misunderstand the complex relations

between the state and the interests involved. For example, the pharmaceutical industry wants more stringent regulation to protect its intellectual property but less stringent regulatory standards for drug toxicology testing. The crucial issues, therefore, revolve around the kind of regulation introduced and enforced, rather than the quantity.

The mission to protect and promote public health laid down in legislation may seem clear. Yet, in this article, I shall demonstrate that, one after another, regulatory agencies have been streamlined and reorganised in order to meet the industry's demands for the marketing of new pharmaceutical products, rather than in *direct* response to public health needs. This may be understood as the operation of the regulatory agency as a 'competition state' which has adopted the industry ideology of international competitiveness and, as a consequence, considers its primary role to be the maintenance of its industry's competitive position in world markets (Cerny 1997; Lofgren & de Boer 2004).

Understanding the emergence of this competition state is important for grasping the nature of the ambitions to harmonise pharmaceutical regulation worldwide and associated debates about whether there is 'global ratcheting-up' of regulatory standards or a 'race-to-the-bottom' (Braithwaite & Drahos 2000). By examining regulatory developments across the European Union (EU), and then between the EU, Japan and the US, I shall explain how the competition state became a building block for the global harmonisation process — a joint industry-regulator enterprise which aims to produce common regulatory standards across the EU, Japan and the US, and beyond, including Australia. As state actors have played a central role in the global harmonisation process, they have needed to legitimise it in relation to their mission to protect and promote public health. For this reason, the competition state does not ignore public health considerations. Rather, it frames industrial interests in public health terms by claiming that the harmonisation process does not lower safety standards, and promises that it

will accelerate the availability of pharmaceutical innovations to patients who need them. However, I shall suggest that these legitimising claims are not tenable.

The competition-nation-state: reshaping public health regulation for commercial interests

Regulation of the pharmaceutical industry grew in the 1970s as regulators became more aware of the tests needed to review modern prescription drugs in the interests of public health. However, the industry had different priorities and sought to establish the ideology that regulatory agencies were 'slow' and 'inefficient' bureaucracies. The first stage in this process was to put forward the claim that regulatory authorities, which took time to check the quality, safety and efficacy of new drug applications, were incompetent and failing to approve new drugs fast enough. During the 1980s, the Association of the British Pharmaceutical Industry complained that the British drug regulatory authorities were inefficient and too slow in approving drugs. The industry claimed that this was detrimental to the British economy because drug development work was going abroad (Abraham & Lewis 2000, pp. 60-1).

In other European countries, the pharmaceutical industry also pressed their drug regulatory agencies to accelerate drug approvals (Anon 1989a). Ultimately, European governments accepted these industry perspectives, though with varying degrees of opposition from their regulatory officials. The emergence of the competition state within pharmaceutical regulation became particularly evident in this period and crucially influenced the nature of the global harmonisation process to come.

In the UK, senior regulators quickly reduced regulatory checks on drug testing, stating that these reductions had become necessary "because early developmental work on new drugs was going abroad to the detriment of British industry" (Griffin & Long 1981, p. 477). By contrast, regulators at the Swedish Department of Drugs

argued that it was not a matter of making an inefficient organisation more efficient, but rather of providing the opportunity for an already effective organisation to cope with the size of its task by recruiting more staff. The implication was that faster approval times did not necessarily equate with efficiency or progress in drug regulation (Anon 1989c; Anon 1989d). Senior staff at the West German regulatory authority blamed the poor quality of many industry applications for the slow pace of the drug review process because deficient applications required additional work to be done by the manufacturer after the approval procedure was under way (Anon 1989e; Anon 1993). They further asserted that the slowness of the regulatory agency in reviewing drug applications did not delay therapeutic advances because the backlog related to products for which equally good therapeutic alternatives existed on the market.

Nevertheless, European governments decided to restructure their drug regulatory authorities in line with the industry's demands, despite the opposition from many European regulators and the fact that industry complaints either had little evidential basis or were irrelevant to drug regulation in the interests of public health. In the late 1980s, the industry proposed that it would be willing to pay the costs of funding drug approvals if this were to result in a "more efficient service" and called for greater informal consultation between companies and regulators (Anon 1987; Anon 1988a; Anon 1988b).

In the UK during the 1970s and 1980s, only about 60% of the annual running costs of the regulatory agency were recouped from the pharmaceutical industry through licence fees, while 40% of funding came from central government taxation. However, in 1989, the UK government accepted the industry's proposal that, in order to make medicines regulation more 'efficient', the regulatory authority should become entirely dependent on fees paid by pharmaceutical companies for licensing. A new industry-funded regulatory agency was created, the Medicines Control Agency (MCA), with its own director who came from the pharmaceutical

industry (Anon 1989f). A concern to protect the commercial interests of the pharmaceutical industry was enshrined within the agency's objectives.

UK Health Ministers also appointed a board of experts, drawn from various quarters including industry and the Department of Health, to advise them on the scope of the MCA's targets and its performance (Anon 1991a). On arrival, the new director, employed on a contract basis, set about establishing 'business units' within the MCA and announced that the agency aimed to reduce the net processing times for new drugs by 24% within a year (Anon 1989b, p. 2). Negotiations over the licensing fees for new drugs revealed the 'exchange' underpinning the new arrangements, and that the priority was the commercial interests of industry rather than careful regulatory review in the interests of public health. For example, industry objected to paying a licensing fee as large as £50 000 for a new drug application without any assurance that their products would pass more quickly through the regulatory system — a sum of £40 000 was finally agreed (Anon 1989g). Yet, from a public health perspective, no such guarantee is possible before reviewing the safety and efficacy data. Leaving no doubt about the purpose of the reforms, the Undersecretary of State for Health told the UK Parliament that reducing the time taken by the MCA to process licence applications was a good investment for the industry, while the Secretary of State for Health welcomed the introduction of the new agency because, he suggested, the Medicines Division had lacked success in providing an effective and efficient service to the industry (Anon 1989h; Anon 1990a, p. 2).

In response to industry complaints, similar changes occurred in Sweden, albeit a decade later, when in 1990 a new regulatory agency, the Medical Products Agency (MPA), was established — entirely funded by fees paid by the pharmaceutical industry (Anon 1990b). The Swedish pharmaceutical industry association found the increased fees acceptable so long as they resulted in faster approval times (Anon

1988a). The industry's concerns about drug approval times achieved a new prominence when specific time frames were recommended in Sweden's Medicinal Product Act which, together with the Medicinal Products Ordinance, came into force on 1 July 1993. This legislation recommended that MPA evaluation of licensing applications for new drugs should be completed within 210 days. In response, the MPA was reorganised into 13 production units, also known as 'results units', developing, in its own words, a working style which is "project orientated and target driven", encouraging frequent consultation with industry (Medical Products Agency 1996, p. 3). Similarly, in 1994, the German Ministry of Health disbanded the existing regulatory agency and replaced it with the Federal Institute for Medicinal Products and Devices (Budesinstitut für Arzneimittel und Medizinprodukte [BfArM]) (Anon 1994). According to the new director of BfArM, it was to be "customer-oriented", meaning industry-oriented, and they were increasing their efficiency despite increased workload (Hildebrandt 1995). By the mid-1990s, BfArM's approval times were among the fastest in Europe (McAuslane 1996).

The proto-competition-supranational-state: European harmonisation

In addition, regulatory agencies have been placed in competition with each other for industry fees and where there are institutional disincentives for non-approval of new drugs. This context was created by the Europeanisation of pharmaceutical regulation. This was not an inevitable result of Europeanisation *per se*, but rather a consequence of the fact that the European Commission largely adopted the industry's vision for Europeanised drug regulation. The transnational pharmaceutical industry is interested in European harmonisation and streamlining of drug regulation because more markets can be accessed more or less simultaneously and subjected to 'efficiency' criteria of fast approval

rates than could be accessed with separate national regulatory regimes. Retrospectively, if not prospectively, European harmonisation may be regarded as the first experiment for the competition state with global harmonisation.

Since January 1998, new drugs can only gain marketing authorisation in more than one EU country in one of two ways — *mutual recognition* or *centralised procedure*. The mutual recognition procedure enables manufacturers to seek simultaneous licensing for a new drug in two or more Member States, providing that they have an existing licence for that drug in at least one Member State, known as the Reference Member State. The regulatory agency of the Reference Member State then approaches the regulatory agencies of the other Member States in which approval is sought. Under this procedure, the regulators in these Concerned Member States are encouraged to agree to license the drug in their countries also, that is, to mutually recognise the initial approval of the Reference Member State. However, if they fail to do so, the matter is referred to the European Commission's scientific advisory body, the Committee for Proprietary Medicinal Products (CPMP) for arbitration. If the CPMP's advice is accepted by the Commission then it is binding on the Concerned Member States and the Reference Member State.

For biotechnology drug products, manufacturers must follow the other route, known as the centralised procedure, which is also optional for highly innovative new drugs. In this procedure, the CPMP and the recently established European Medicines Evaluation Agency (EMA) simply decide whether an EU-wide licence for the drug should be approved after considering the assessments by a rapporteur regulatory agency. Any objections by other Member States to the rapporteur's assessment are considered by the CPMP, who then make a recommendation, which is binding on Member States, for or against an EU-wide licence.

To accommodate the industry's desire for more rapid approval times, strict time scales have been prescribed by the European Commis-

sion for the mutual recognition procedure, namely 210 days. Moreover, the largest amount of regulatory work (and hence fees from industry) is generated by Reference Member State status within the mutual recognition procedure, and rapporteur status in the centralised procedure. As the regulatory agencies in the EU are now largely funded by industry fees for their regulatory work, and because companies look for fast approval rates as one of their key criteria when choosing a Reference Member State, the regulatory agencies of Member States are, in effect, competing with each other for 'regulatory business' by attempting to approve drugs at an ever faster pace.

The competition for fees from industry means that regulatory agencies are not even satisfied to meet the European Commission's requirement of approval (or non-approval) within 210 days. For example, the average net in-house assessment times by the MCA for new drugs fell from 154 working days in 1989 to just 44 days by 1998. The drug regulatory review times for Germany, Sweden and other EU countries have also fallen dramatically (Abraham & Lewis 2000). It might be argued that this competition between regulatory agencies will drive up the quality of regulatory review of drug safety and efficacy. However, even if such competition were to encourage some regulatory agencies to try to improve their safety and efficacy regulation relative to others, this will occur in a context in which all EU regulatory agencies have increasingly less time to check the drug safety and efficacy data submitted by companies. According to some regulators, the consequences of ever faster regulatory reviews present dangers to public health. They note that the drive to accelerate regulatory reviews compromises the independence of regulatory agencies from industry because it leads to excessive trust being invested in the documentation submitted by manufacturers.

The suggestion that such interagency competition is driven by a concern to improve the quality of safety and efficacy regulation is further undermined by the fact that a very different approach has been taken towards *rejections* of

new drug applications and 'old' unproven products on the market. The Swedish regulatory agency *extended* the response period for a company whose product licence application faced rejection from 6 weeks to 3 months. Meanwhile, in Germany, 'old' products, whose efficacy had never been demonstrated against the modern standards of the 1976 German Drug Law, were granted *extended* 'licences of right' to 2004. Despite the potential disadvantages of these measures for consumers and patients, they were not regarded by the government authorities as 'inefficient' (Abraham & Lewis 2000).

Evidently, the time taken for regulatory processes and decision making may be *extended*, rather than *accelerated*, if this is in the interests of the industry.

Moreover, under the mutual recognition procedure, a heavy emphasis on widening new drug approvals co-exists with institutional disincentives to block approval. If a Member State does not wish to mutually recognise the new drug approval of another Member State on risk to public health grounds, it must immediately inform the company, the Reference Member State, the Concerned Member States and the Committee for Proprietary Medicinal Products, stating the reasons for its decision and indicating how the gaps in the new drug application might be filled in such a way as to facilitate mutual recognition. A compulsory conciliation stage then follows to facilitate the Member State's recognition of the Reference Member State's approval (Abraham & Lewis 2000). Thus, regulators are under pressure to adopt quickly a position on the Reference Member State approval and to assemble robust evidence to support that position if they propose to *reject* an application on grounds of risk to public health. There is no such pressure if they intend to mutually recognise the Reference Member State's approval.

The international regulatory network-state: ICH

More generally, the transnational research-based pharmaceutical industry has successfully lob-

bied for the creation of property rights in test data submitted to regulatory agencies as part of the marketing approval process. The main purpose of this has been to delay the entry of generic drugs into the market. The creation of such exclusive rights makes regulation for public health more, not less, difficult (Correa 1999).

In this section, I examine a network of pharmaceutical industry and government scientists who have, in effect, become the international regulatory power in setting the safety standards for new medical drugs. It currently represents the greatest expression of the competition state within the global harmonisation process. It is known as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The key participants are the three pharmaceutical industry associations and three government drug regulatory agencies of the EU, Japan and the US — who often refer to themselves as ‘the six-pack’ — and actually comprise 17 countries, of which 15 are the pre-2004 accession member states of the EU. The EU, Japan and the US are the three largest pharmaceutical markets in the world. Of the US\$22.7 billion spent worldwide on pharmaceutical research and development (R&D), they spent 90 per cent (Nakajima 1996, p. 32).

Between 1991 and 2004, the ICH has developed guidelines on drug safety for new drug approval, which the government regulatory agencies of the EU, Japan and the US invariably adopt. In addition to the ‘six-pack’ participants, there are also some ‘observers’, including representatives of Canada, the European Free Trade Association (EFTA), which comprises Norway, Iceland and Liechtenstein, and the World Health Organisation (WHO). Thus, adoption of ICH guidelines may go beyond the EU, Japan and the US. For example, the Australian, Canadian and EFTA drug regulatory authorities have already adopted some ICH guidelines, and WHO officials have indicated that, in the long term, the results of ICH may provide a basis for the revision of WHO guidelines on clinical evaluation of new drugs (Anon 1992).

The ICH process focuses on risk-benefit assessments of drugs and the management of drug safety data. However, the drive to harmonise these matters internationally, and the nature of such harmonisation, needs to be seen in a broader political and economic context. As with the emergence of the competition nation-state and supranational state, trade, international market competition and the structural interests of the pharmaceutical industry have been, and remain, key motivating factors. In the mid to late 1980s, bilateral initiatives between the governments of the US and Japan were taken, including a determined objective on the part of the US to open up Japanese markets. Specifically, a conference in 1985 between the American and Japanese governments on an ‘Action Plan for Improved Market Access’ committed the Japanese drug regulatory authorities to some international harmonisation with the US for the first time (Ferris 1992, pp. 197-8). Japan represents about 22 per cent of the world pharmaceutical market (Reed-Maurer 1994, p. 38). In response, the European Commission strengthened its resolve that there should be a single EU market which could compete with Japan and the US in R&D and international trade negotiations (Wyatt-Walter 1995). This had two effects: the project of international harmonisation of regulation *within* the EU was taken much more seriously at all levels of industry and government; and in 1988 the first ‘mission’ of government regulators and industry representatives from the pharmaceutical sector in Europe was sent to Japan to discuss bilateral harmonisation of regulation between Japan and the EU, so that Japanese markets might become more accessible to the European industry. However, given the importance of the US market, the European pharmaceutical industry was unenthusiastic about solely bilateral harmonisation with Japan. Consequently, the International Federation of Pharmaceutical Manufacturers’ Associations (IFPMA) took responsibility for organising trilateral meetings between the industry and government regulators in the pharmaceutical sectors of the EU, Japan and the

US, which became known as ICH during the 1990s.

Since the 1950s the strategy for success pursued by pharmaceutical companies has been to invest in R&D followed by extensive marketing that could generate profits for further R&D. According to McIntyre (1999, pp. 17, 49), between 1972 and 1997 the R&D expenditure of the British pharmaceutical industry grew from £42 million (7 per cent of gross output) to £2251 million (21 per cent of gross output). Yet the growing complexity of the diseases and illnesses, which remained after the antibiotic era of the 1940s and 1950s, increased the duration of R&D as well as its expense. The cost to bring a new chemical entity to market can be as high as US\$350 million and it is estimated that the time from first synthesis of a new drug to its marketing quadrupled from 1960 to 1989 (Halliday et al 1997, p. 63; Tansey, Armstrong & Walker 1994, p. 85). As patents are awarded when compounds are first synthesised, the consequence of longer R&D times is that companies' new drugs have shorter periods of patent-protected market exclusivity during which to maximise returns on investment and make profits. Moreover, the industry experienced a decline in productivity in terms of the number of new chemical entities launched on the market between 1975 and 1990 because of the increased rate of failure in increasingly complex experiments, and because of more exacting regulatory requirements (Poggiolini 1992, pp. 13-14).

In response, the industry strove to decrease the cost and duration of R&D by reducing regulatory requirements imposed by the state, including those concerned with safety and efficacy testing, and to reach larger markets more effectively. Such transnational firms could get better returns on R&D investments if they could access international markets more or less simultaneously, but faced increased costs if they had to cope with separate, and sometimes divergent, national regulatory regimes (McIntyre 1999, p. 96). By the late 1980s, the European Commission had accepted the argument put forward by

the European pharmaceutical industry that it was significantly constrained by the lengthy and differing drug registration procedures of the EU Member States (Cecchini 1988). According to the Director-General for Industry at the European Commission, the role of the Commission in the pharmaceuticals area is "to provide an appropriate legal and regulatory environment geared towards fostering industrial co-operation" by "removal of legal barriers" (Micossi 1998, p. 40).

With the intra-EU 'experiment' in harmonisation growing in viability, in the context of the inter-regional concerns about market competition mentioned above, a similar argument was applied more globally in the form of ICH, involving the industry representatives and regulators from the EU, Japan and the US as main voting parties and representatives from the Canadian regulatory agency, the WHO and the EFTA as non-voting observers. Indeed, some in industry regard ICH as the first step towards global harmonisation and the production of a global registration dossier which would contain all the data needed for marketing approval in any country in the world (Anon 2000). A further goal is the mutual recognition of marketing approval across the three regions (Giaquinto 1998, pp. 554-8; Deboyser 1998, pp. 558-62). It has even been suggested that new drugs approved by the 'six-pack' might simply be approved administratively by developing countries without additional review of the data by their governments (Poggiolini 1992, p. 18).

While these industrial and trade interests have motivated pharmaceutical harmonisation, the ICH process is also often linked to the interests of patients and public health by those who support harmonisation. At the opening session of the first ICH conference in Belgium in 1991, it was argued that the savings made by companies from harmonised regulations would further the delivery of innovative research yielding therapeutic benefit to patients (Bangemann 1992, p. 4). Four years later, at the opening of the third ICH conference in Yokohama, the Director-General of the Japanese drug regulatory authorities

declared that “patients should be given the highest priority”, and that “the judgement criteria for any discussions in ICH are — is this for the benefit of patients?” (Araga 1996, p. 19). The secretariat of the ICH contended that “the urgent need” for harmonisation was “impelled” by “the need to meet the public expectation that there should be a minimum of delay in making safe and efficacious treatments available to patients in need” (IFPMA 1998). By the end of the decade, they were making even more emphatic claims in this respect:

ICH clearly enhances the competitive position of those companies that choose to operate using its standards, as well as significantly benefiting both the regulators and the patients, who, most importantly, receive crucial new treatments sooner . . . In summary, harmonisation through ICH brings important, life-saving treatments to patients faster, while releasing the pharmaceutical companies’ development funds to projects that will produce the groundbreaking treatments of the future (IFPMA 2000, p. 1).

Such pronouncements helped to give the ICH process a much broader societal credibility. By representing it as being in the interest of public health, it became legitimate for governmental regulatory agencies, who are supposed to protect public health, to become its allies. Indeed, a significant justification for government regulators’ involvement in ICH is that the rationalisation process entailed will contribute to public health.

Safety standards and public health: the case of adverse drug reaction reporting

The ICH has produced dozens of guidelines. For the purpose of brevity, I focus here on just one safety guideline concerned with the reporting of adverse drug reactions (ADRs). This guideline has been adopted by the Australian drug regulatory agency as well as that of the EU, Japan and the US. Contrary to what IFPMA (2000, p. 7)

seems to claim, ICH guidelines involve more than solely the eradication of duplicative testing: they also imply a *reduction* in regulatory safety checks, as this case study will demonstrate.

While a drug is being tested in clinical trials, and after a new drug has been marketed, its risks to patients are monitored by reports from doctors about adverse reactions to the drug. In the case of clinical trials, the clinical investigator is responsible for recording all ADRs under the supervision of the manufacturer. After the drug is on the market, prescribing doctors may voluntarily report ADRs to the manufacturer or directly to the government regulatory authorities. The ICH guidelines, which we consider here, are concerned with requirements on pharmaceutical companies to report to regulatory agencies in a timely manner ADRs that come to their attention. This is important because if a drug is associated with many more, or more serious, adverse reactions than others in its therapeutic class, then it may be that its risks outweigh its benefits and it should be withdrawn from the market by regulators.

As regulatory agencies cannot make timely decisions to withdraw or suspend drugs from the market without adequate information about ADRs, there is clearly a great deal of regulatory trust in industry. However, in the past this regulatory trust has been breached, as occurred with Halcion and Opren/Oraflex (Abraham 1995; Abraham & Sheppard 1999). In such cases, transnational pharmaceutical companies often attempt to justify failures to provide regulatory agencies with timely ADR reports because of poor communication between different parts of the company. The ICH process, therefore, presented an opportunity to harmonise safety standards upwards in this respect so that such justification could no longer be countenanced. Yet the guidelines do not make clear that companies bear full responsibility for the conduct of any foreign subsidiaries.

Furthermore, there have been cases of large increases in the occurrence of known ADRs, but they have not been reported in a timely manner by the pharmaceutical companies on

the grounds that they did not reflect a “meaningful change in ADR occurrence or safety profile”. However, that judgement by scientists in industry was not shared by regulators when they discovered it. Leaving the matter of what counts as a significant change in risk to subjective judgement in this way is insufficiently protective of public health and has been proven to be so in the past (Abraham 1995). A clear internationally harmonised quantitative standard to counter this problem could have been developed at ICH. However, regarding ‘expected’, serious ADRs, ICH recommended that “an increase in the rate of occurrence, which is judged to be clinically important,” should be reported to regulators, “as opposed to a more quantitative approach” (ICH 1994; Gordon 1994, p. 384). Similarly, for other ADRs, ICH comments:

Increase in the frequency of reports for known ADRs has traditionally been considered as relevant new information. Although attention should be given in the periodic safety update report [PSUR] to such increased reporting, no specific quantitative criteria or other rules are recommended. Judgement should be used in such situations to determine whether the data reflect a meaningful change in ADR occurrence or safety profile (ICH 1996, p. 3).

It is notable that the US Food and Drug Administration (FDA) requires *quarterly* PSURs during the first 3 years of marketing, while the EU and Japan require PSURs only *every 6 months*. Yet ICH made no attempt to harmonise these requirements upwards to the FDA’s standards so as to maximise protection of public health.

Regarding which kinds of ADRs require expedited reporting to regulators, the ICH has also fallen considerably short of the highest level of safety checks available on the international scene. Before ICH, 12 of the 17 countries in the ‘six-pack’ required expedited reporting (ie, within a matter of days) of serious ADRs even if they were expected reactions with the new drug, while 4 of the 17 required such

reporting of non-serious ADRs if they were unexpected. One of the 17 countries required expedited reporting of non-serious ADRs that could be expected (Garutti 1994, p. 376). However, ICH recommended that expedited reporting to regulators “is not generally appropriate for expected, unrelated, or non-serious cases” (Gordon 1994, p. 384). In other words, ICH opted for the *lowest* common denominator on this safety issue. This approach to guidelines permits industry to interpret regulation with a flexibility that does not increase protection of public health.

Moreover, the ICH experts initially proposed that fatal and life-threatening ADRs should be reported to regulators within 5 days. However, after the Japanese industry association argued that this was “quite impractical”, the ICH guideline was altered to require such reporting within 7 days (Okuno 1994, pp. 401, 406). The change was made even though a committee of the Central Pharmaceutical Affairs Council in the Japanese regulatory authority urged that there was a need to strengthen information collection and dissemination about drug product safety in Japan (Anon 1995). The committee’s concerns and the problems of regulatory trust are highlighted by the Japanese Pharmaceutical Manufacturers’ Association’s introduction of a code of conduct aimed at eliminating corruption and collusion between doctors and drug companies following a number of bribery cases in Japan (Ross 1994a). In late September 1994 a research report by the leading Japanese newspaper *Mainichi Shimbun* quoted unnamed drug company executives as saying that Japanese drug companies often suppress or disregard data on potential ADRs if the information is deemed harmful to marketing efforts (Ross 1994b). Such revelations coincided with this ICH guideline which invests greater, not less, trust in drug companies.

The loosening of regulatory standards regarding this safety check is not atypical: a similar process has been demonstrated for other ICH safety guidelines (Abraham & Reed 2001).

Conclusion

In political terms, the active role of state regulators and government departments together with the privileged position of industry above all other interests in this harmonisation process signals a form of corporatism at work, rather than regulatory capture or pluralist pressure-group lobbying. Furthermore, the positioning of regulatory agencies in competition with each other for regulatory business via fees from industry indicates a neo-liberal context for corporatism. Hence, the regulatory state in the pharmaceutical sector, at the national, supranational and global-network levels, is characterised by neo-liberal corporate bias — and this is largely because it has taken on the role of a competition state. The evidence suggests that such a regulatory state, and its associated ambitions of global harmonisation, is not consistent with the best interests of public health. In particular, safety standards are reduced and the promise of increased innovations needed by patients is unpersuasive in a regulatory context which does not require manufacturers to demonstrate that their new products are more therapeutically effective than products already on the market.

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