

**Regulatory Interdependence In A Global Economy:
The Globalization of Pharmaceutical Regulation
In the EU and Internationally**

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ABSTRACT

Historically drug regulation has been virtually synonymous with national sovereignty. Over the last decade, this has begun to change: national regulatory agencies are more closely cooperating with one another. The European Union has established a centralized drug approval system; the United States Food and Drug Administration has begun to accept foreign clinical data; and a number of industrial nations have made substantial progress toward standardizing their regulatory procedures and requirements.

This paper describes and assesses the implications of recent developments in the international coordination of national drug approval policies. It specifically examines the emergence of a single market for pharmaceutical products in the European Union, the globalization of American drug approval policies, and the accomplishments of a new international body, the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical Products (ICH).

I. INTRODUCTION

Drugs have long been among the most extensively regulated of all consumer products. Not only do all governments closely supervise virtually every aspect of their development, testing, production and marketing, but many also regulate their pricing and distribution. While the pharmaceutical industry is highly globalized -- over half of the total sales of the fifty largest drug companies are made outside their home country -- firms have been required to conduct separate tests, submit separate applications, and meet distinctive criteria to enter each national market.

Historically drug regulation has been virtually synonymous with national sovereignty. Over the last decade, this has begun to change: national regulatory agencies are more closely cooperating with one another. The European Union has established a centralized drug approval system; the United States Food and Drug Administration has begun to accept foreign clinical data; and a number of industrial nations have made substantial progress toward standardizing their regulatory procedures and requirements.

This paper describes and assesses the implications of recent developments in the international coordination of national drug approval policies. It specifically examines the emergence of a single market for pharmaceutical products in the European Union, the globalization of American drug approval policies, and the accomplishments of a new international body, the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical Products (ICH).

This case-study of the globalization of regulatory policy illustrates several aspects of the dynamics of international regulatory coordination and cooperation. First, such coordination is a complex and difficult process, particularly for products with significant health and safety dimensions. Secondly, there are many dimensions to coordination, ranging from information exchanges to agreement on testing protocols to the mutual recognition of product approvals. Regulatory

cooperation is best understood as a cumulative, gradual process. Thirdly, the undermining of national regulatory sovereignty can strengthen the effectiveness and efficiency of national regulation: trade liberalization and regulatory reform are often mutually re-enforcing.

THE EUROPEAN UNION

The Scope of the Problem

Separate national drug approval policies and requirements have long presented a critical obstacle to European integration.¹ According to a 1988 European Commission report on the single market (the Cecchini report), the European pharmaceutical industry was significantly constrained by the "lengthy and differing drug registration procedures" of the Member States.² Moreover, "all pharmaceutical companies . . . treat the Member States as separate markets."³ Some multinational firms did not even bother to apply for product approval in each member state, and most smaller firms limited their product marketing to their own country.

Distinctive national registration requirements imposed substantial costs on governments, since each was required to maintain its own regulatory bureaucracy. In 1993, the EC's twelve Member States employed 2,000-2,500 full-time drug evaluation staff, plus about 1,000 expert consultants. The annual cost of twelve separate national drug authorities was approximately \$300 million, a cost borne directly by pharmaceutical manufacturers, since they pay for clinical trials as well as registration and

¹ The first move toward European drug harmonization dates to 1965 and directive 65/65/EEC, prescribing criteria for premarket approval. See Richard Kingham, Peter Bogaert, and Pamela Eddy, "The New European Medicines Agency," The Food and Drug Law Journal, Vol. 49, iss. 2, 1994, p. 301.

² Luis Oraz, Kenneth Kaitin and Louis Lasagna, "Pharmaceutical Regulation in the European Community: Barriers to Single Market Integration," Journal of Health Politics, Policy and Law, vol. 17, no. 4 (Winter 1992), p. 849.

licensing fees⁴. Since regulatory approval costs are linked to clinical testing rather than to market potential, many firms avoided smaller markets altogether.⁵ Drug approval policies varied significantly throughout Europe, due to cultural factors, the degree of acceptance of folk remedies, religious beliefs and the differences in the assessments of risks and benefits by regulatory authorities. Member States also differed in the speed with which they approved new drugs, further complicating marketing in what is potentially the world's largest pharmaceutical market. For example, approval in England and France could be gained in less than one year while Germany regularly took up to five.⁶

However, Member States were reluctant to surrender their historical control over drug approval. This is due not only to their distinctive regulatory styles and traditions, but also to the close ties between drug approval policies and national health care policies -- and thus to national budgets. Approximately half of the industry's revenues in Europe come from national governments. In addition to controlling new product registration, Member States control drug prices and subsidize development costs, making this industry among Europe's most extensively and closely regulated.⁷ When the European Community was established, health care, like all other aspects of welfare policy, was left exclusively to the Member States.⁸

³ Ibid.

⁴ "Why Europeans are being Shorted on Miracle Drugs," Wall Street Journal, April 18, 1994, p. A13.

⁵ J. Howells, "Pharmaceuticals and Europe 1992: The Dynamics of Industrial Change," Environment and Planning, vol. 24 (1992) p. 36.

⁶ Daniel Green, "EU Body to Speed Up Approval of New Drugs," Financial Times, January 26, 1995, p. 2.

⁷ A.J.W. van de Gevel, "The Pharmaceutical Industry," CEPS working paper number 42, June 17, 1992, p. 5.

⁸ Tessa Richards, "Medicine in Europe: 1992 and all that," British Medical Journal, vol. 303 (November 23, 1991), p. 1322.

As one student of EU drug policy noted in 1989:

The free movement of drugs in the European Community is not only hindered by the fact that the national competent authorities render different value judgements on the merits of therapeutic approaches and on issues of relative benefits and risks of drugs. On top of these drug-specific differences come *health-policy-specific* differences in the control of the social-security system, and *industry-specific* differences in the control of the drug industry's prices and profits, and differences in the extent to which national governments assist their national drug industry.⁹

The Financial Times observed in 1990 that:

If you suffer from stomach problems and live in France or Germany, do not ask your doctor to prescribe Zantac, the world's best-selling medicine. The product, made by Britain's Glaxo, is called Azantac in France; in Germany it is Zantic. The linguistic distinctions are a symptom of the difficulties faced by western Europe's 30 billion-pounds-a-year pharmaceuticals industry in moving to a single market . . . Such fragmentation has the effect of imposing trade barriers of the kind that 1992 is supposed to eliminate.¹⁰

Initial Efforts

The efforts to reduce national disparities in drug regulation began in 1963, when the European Commission convened a conference of industry representatives, doctors, and consumers to discuss standardizing pharmaceutical laws.¹¹ However, there was disagreement over whether a drug should have proven "therapeutic potency" before it could be authorized. While doctors, pharmacists, consumers, and trade union representatives argued that this requirement was indispensable, industry representatives refused to accept it.¹² The result was stalemate.

In 1965, the EU issued its first pharmaceutical directive, It established baseline "criteria for

⁹ Erich Käufer, "The Regulation of Drug Development: In Search of a Common European Approach," EUI Working Paper No. 89/411, Florence: European University Institute, October 1989, p. 20.

¹⁰ Peter Marsh, "A Suitable Case for Treatment," Financial Times, August 22, 1990, p. 17.

¹¹ Luis Oraz, Kenneth Kaitin and Louis Lasagna, "Pharmaceutical Regulation . . ." op. cit., p. 853.

¹² European Community Commission, press release IP (63) 156, September 16, 1963.

safety, quality and efficacy as preconditions for marketing authorization for new drugs."¹³ The directive also defined medicinal products and required Member States to ensure that submissions of medicinal products to national authorities were prepared and signed by experts with "the necessary technical or professional qualifications." These qualifications, however, remained undefined.¹⁴ Moreover, the efficacy test itself was restricted: "Therapeutic efficacy would only be considered lacking in a medicine which failed to produce pharmacodynamic results."¹⁵ "Pharmacodynamic" was defined as "*any response* by a living organism to the introduction of a pharmaceutical".¹⁶ Yet even this minimal qualification was enacted by only seven of the twelve Member States.¹⁷

In 1974 the European Commission drafted a directive that permitted only "qualified persons" to supervise drug production. But the Commission ultimately adopted such a wide definition of qualified person (a medical man, a veterinarian, a chemist, a pharmaceutical technologist, or a biologist) so as to make the directive meaningless.¹⁸ Thus, through the mid-1970s, virtually no progress had been made in creating a single market for pharmaceutical products.

A New Approach

In 1975, the EC established the Committee for Proprietary Medicinal Products (CPMP), with

¹³ Ibid, p. 854.

¹⁴ Directive 65/65 EEC, Quoted in Luis Oraz, Kenneth Kaitin and Louis Lasagna, "Pharmaceutical Regulation..." op. cit., p. 853-854.

¹⁵ Leigh Hancher, Regulating for Competition: Government, Law, and the Pharmaceutical Industry in the United Kingdom and France, Oxford: Clarendon Press, 1990, p. 109.

¹⁶ Webster's Ninth Collegiate Dictionary. New York: Mirriam-Webster, 1978. Emphasis added.

¹⁷ Luis Oraz, Kenneth Kaitin and Louis Lasagna, "Pharmaceutical Regulation..." op. cit., p. 854.

¹⁸ Ibid.

members drawn from the regulatory authorities of the Member States¹⁹. The CPMP was given the authority to review all drug applications to EU Member States. Applications would be examined for conformity to European Union safety, quality, and efficacy standards, and the Committee would then issue an opinion on marketing approval.²⁰ Unlike the FDA, however, the CPMP's role was only advisory. Member States maintained the right to deny approval of a pharmaceutical product even if the Committee recommended approval.²¹

The EC also established a multistate procedure for drug approval. This process, variously referred to as the "multi-state," "the decentralized" or the "concurrent application" procedure, was initially established in 1975 and later revised in 1983.²² Under the multi-state process, a manufacturer would first submit its product to any national pharmaceutical regulatory agency. If that body granted approval, the company could then submit "concurrent applications" to at least five other Member States. The latter, in turn, were required to take the initial authorization into account in their own review, thus presumably expediting their approval process. If a member state refused authorization, it was required to submit a "reasoned objection" to the CPMP within three months. The CPMP would then have two months to issue an opinion on the objection. But final approval still resided with the regulatory bodies of each member state.

But the establishment of multi-state procedure had little impact on national drug approval policies. German firms boycotted it "as a matter of principle."²³ Although Member States were only

¹⁹ Luis Oraz, Kenneth Kaitin and Louis Lasagna, "Pharmaceutical Regulation . . ." p. 855.

²⁰ Teresa Buono, "Biotechnology-Derived Pharmaceuticals . . ." p. 145.

²¹ Luis Oraz, Kenneth Kaitin and Louis Lasagna, "Pharmaceutical Regulation . . ." p. 855.

²² See Rosemary Kanusky, "Pharmaceutical Harmonization in the United States, the European Economic Community and Japan," Houston Journal of International Law vol. 16 (1994), p. 677.

²³ A.J.W. van de Gevel, "The Pharmaceutical Industry," p. 5.

supposed to reject CPMP recommendations in "exceptional cases," and after making "reasoned objection," such objections in fact became the norm. Only half of the licenses originally granted by a member state were accepted by the other Member States to which they were submitted.²⁴

The multi-state procedure was intended not only to generate confidence among Member States about each other's scientific competence, but also to speed the approval of safe and effective drugs. Results were mixed for this goal as well. Since the multi-state procedure had strict time limits (a state had 4 months to evaluate a dossier that another state had already approved) Member States did give priority to multi-state applications. However, because Member States still carefully investigated each application rather than relying on the initial state's opinion, the multi-state time limits were frequently violated.²⁵ Only in France were the time limits ever approached. In Germany and the United Kingdom the delay was more like two years, and in Italy, Spain, the Netherlands, or Belgium the delay was three years or more.²⁶

Consequently, there was no real progress towards mutual recognition. As the Committee's chair noted in 1988, "Each concerned state seemed to conduct its own assessment and raised its own objections In practice there have been objections with regard to each and every case dealt with under the Multi-State procedure." He concluded that "on the whole, the Member States do not yet accept each other's assessments."²⁷

²⁴ Ibid, p. 6.

²⁵ Ibid.

²⁶ J. Howells, "Pharmaceutical and Europe 1992: The Dynamics of Industrial Change," *Environment and Planning* vol. 24 (1992), p. 34.

²⁷ CPMP (Committee for Proprietary Medicinal Products), Contributions for a Future Marketing Authorization System, III/3785/88 Brussels: Commission of the European Communities, 1988. Quoted in Luis Oraz, Kenneth Kaitin and Louis Lasagna, "Pharmaceutical Regulation..." op. cit., p. 856.

Toward Harmonization

In 1987, the European Council, frustrated by the ineffectiveness of the multistate procedure and committed to the Community's goal of creating a single European market by 1992, chose a radical new approach. It approved a directive establishing a CPMP-administered "Centralized Procedure." This procedure was designed especially for biotech and high technology products, since Brussels reasoned that it would be easier to harmonize standards that had not yet been created than to force states to change their existing ones. The CPMP pooled scientific expertise in this new area of medical research in order to create a Europe-wide consensus as to what constituted good manufacturing practices, appropriate laboratory procedures and appropriate evaluation criteria.²⁸

Once a manufacturer submitted its application, the CPMP had seven months to complete its initial evaluation; firms were then required to respond to both CPMP and Member States' concerns within three months. The Member States would then have up to one month to make their final recommendations, following which the CPMP would send its report to all additional parties.²⁹ While the CPMP's report was nonbinding, this new procedure was intended as the first move towards genuine supra-national evaluation: "While fundamentally national, it [was] seen by the Commission as a significant step in the direction of a single evaluation procedure applicable throughout the Community."³⁰

Following approval of the Maastricht Treaty on European Union (1992), which gave the EU

²⁸ Fernand Sauer, "Harmonization of Biotechnological Regulations in the European Community," in Chiu and Gueriguian, eds., Drug Biotechnology Regulation: Scientific Basis and Practices (1991), pp. 455, 460.

²⁹ Rosemary Kanusky, "Pharmaceutical Harmonization . . ." p. 681.

³⁰ CPMP (Committee for Proprietary Medicinal Products), Contributions for a Future Marketing Authorization System, III/3785/88 Brussels: Commission of the European Communities, 1988. Quoted in Luis Oraz, Kenneth Kaitin and Louis Lasagna, "Pharmaceutical Regulation . . ." op. cit., p.

binding authority on some health care issues, the European Commission undertook another major new initiative to harmonize national drug approval policies.³¹ It established a new regulatory institution, the European Medicines Evaluation Agency (EMA) and two new regulatory procedures.³² The EU's goal was to significantly transform the relationship between national regulatory authorities and those of the Union, thus finally creating a common market for pharmaceutical products.

The centralized application procedure placed final regulatory approval at the Union level for the first time. It permitted manufacturers to submit applications directly to the European Agency, which then refers them to the CPMP for evaluation. The latter is required to issue its opinion within 210 days. If approval is denied, the drug's sponsor may file an appeal, which in turn must be reviewed within sixty days. Final approval rests with the European Commission, which has ninety days to draft its own opinion. If the Commission grants marketing authorization, it automatically becomes valid throughout the EU for renewable periods of five years. The EMA centralized approval process was designed to be relatively rapid, with application to final approval to take a maximum of ten months.³³ This is more than twice as fast as that of many member state drug regulatory agencies. To help the EMA meet its own deadlines, applications could be accepted on CD-ROM, and the agency's recommendations were to be distributed by e-mail.³⁴

856.

³¹ See article 129 of the Maastricht Treaty on European Union (1992). Quoted in "How should European Health Policy Developed?" *British Medical Journal*, vol. 309 (July 9, 1994), p. 116.

³² The EMA consists of the CPMP, the corresponding body for veterinary medicine, "a secretariat, an executive director, and a management board composed of representatives of the Member States, the Commission, and the European Parliament." Kingham, et. al, "New European Medicines," p. 303.

³³ Kingham, et. al, "New European . . .," p. 307.

³⁴ Daniel Green, "European Medicines Evaluation Agency: Fast-track Approvals Service," *Financial Times*, April 25, 1995, p. 13.

The centralized procedure specifically targeted biotechnology drugs, which must be approved by EMEA, as there is no national alternative.³⁵ Biotechnology has been targeted because of its potential for economic growth and, because since it is such a new field, individual states have not yet created their own testing infrastructures.³⁶ As one European official explained, "Global participation means we don't have to keep on reinventing the wheel. A new technique such as stereoisomerism, for instance, offers the chance to put together a unified international approach *before* separate guidelines are issued The most obvious candidate here is biotechnology."³⁷ Manufacturers of other pharmaceutical products may also elect to use the centralized procedure.³⁸

The Union also established a decentralized procedure open to all pharmaceutical products, except those produced through biotechnology.³⁹ This procedure, based on the principle of mutual recognition, was enacted into law in 1993 and went into effect on January 1, 1995. If a product has been approved for use in any member state, its manufacturer may submit an identical scientific and technical dossier to any or all other Member States. It also must notify both the CPMP and the member state to which its application was first submitted; the latter then is required to furnish its assessment report to each country where recognition is sought. Each member state then has ninety days to decide whether to recognize the first nation's approval. It must do so unless, "there are grounds for supposing

³⁵ Daniel Green, "EU Body . . ." p. 2.

³⁶ Teresa Buono, "Biotechnology-Derived Pharmaceuticals . . ." p. 134.

³⁷ Unnamed European official, "Global harmonization on Pharmaceutical Regulations a Step Nearer," Pharmaceutical Business News, November 15, 1991. Available on NEXIS, europe library.

³⁸ Rosemary Kanusky, "Pharmaceutical Harmonization . . ." p. 699.

³⁹ Richard Kingham, Peter Bogaert and Pamela Eddy, "The New European Medicines Agency," Food and Drugs Law Journal Vol. 49, Issue 2, 1994, pp. 309 - 312.

that the authorization of the medicinal product concerned may present a risk to public health."⁴⁰ In cases of disagreement, Member States are encouraged to solicit the opinion of the CPMP.

While firms may still apply to individual Member States for marketing approval, beginning on January 1, 1998, any member state which receives an application for a product which has been approved by another member of the Union, must either recognize that approval, or refer the application to the CPMP for binding arbitration. Thus pharmaceutical products will, for the first time, be subject to mutual recognition, under the auspices of the EMEA.

Unlike the FDA, the EMEA's role is a coordinating one; the actual processing of applications was delegated to national regulatory agencies. This in turn means that the agency must rely on member state authorities not only to process applications in a timely fashion, but also to apply similar standards. The harmonization of national requirements is even more critical for the viability of the EU's decentralized procedure, since under this procedure a single national authority will be able to approve a product for the entire EU. According to Fernand Sauer, the agency's executive director, "after 15 years of harmonization we now have everything in place so that EMEA and all of the national authorities practice exactly the same requirements."⁴¹ The inspection of manufacturing facilities and the certification of the reviewers of applications will also depend on national authorities.

Both new procedures promise to provide important benefits to manufacturers. Streamlined approval allows cash flow to start sooner. "Successful new drugs earn \$1 million per day in global sales revenues. The European Union accounts for about 40 percent of global sales."⁴² Also, more rapid drug approval will increase the effective life of drug patents, enhancing the expected value of

⁴⁰ Quoted in *ibid*, p. 311.

⁴¹ Wayne Koberstein, "Fernand Sauer: Tending the Garden," Pharmaceutical Executive January 1996, p. 46.

future research.⁴³ And since companies can submit one application rather than 15, large firms may save up to \$5 million annually in national clinical staff and testing equipment.⁴⁴ While the application fee for submitting a drug to the EMEA is high - a typical filing costs approximately 200,000 ECUs - this is about half of what it would cost to pay all fifteen national fees. Centralized approval will also enable firms to use identical package inserts and make similar promotional claims throughout the EU. It is also likely to promote more European-wide drug research and development.

The EMEA in Operation

Although delayed for a few months by a last-minute debate over its fee structure, the European Agency opened its doors to great fanfare on Canary Wharf in London on January 26, 1995.⁴⁵ The EMEA will operate on an experimental, yet fully authoritative basis until 1998. Its 1995 budget was 9.5 million ECUs, but through registration and annual fees, the Agency is expected to be self-supporting by 1998 and anticipates a budget of 50 million ECUs by 2000.⁴⁶ Its staff will remain relatively small because the EMEA will coordinate with teams of experts from EU member state drug approval boards, whose combined staff of over 1,600 will actually conduct the drug evaluations.⁴⁷ Nonetheless, this represents a 50% reduction in the national regulatory staffs from pre- to post-EMEA

⁴² Daniel Green, "European Medicines . . ." p. 13.

⁴³ Daniel Green, "EU Body . . ." p. 2.

⁴⁴ Estimate by Nick Bosanquet, Professor of Health Policy at Imperial College, London. Quoted in Daniel Green, "EU Body . . ." p. 2.

⁴⁵ "See "Internal Market Council: Belgium Opposes Medicine Evaluation Agency," European Report, December 10, 1994; and Susan Perry, "Drugs Companies Alarmed by EU Medicines Agency Delay," Reuter European Community Report, December 28, 1994.

⁴⁶ Ben Hirschler, Reuter European Community Report, July 4, 1994.

⁴⁷ Ibid.

levels.⁴⁸

European industry has been generally supportive of the EMEA. European Federation of Pharmaceutical Industries Association President Kurt Briner stated:

Our task is to produce high-quality medicines for patients. The agency's task is to bring into operation a high-quality, high-performance, efficient registration mechanism that gives patients speedy access to those products . . . The credibility of Europe, its pharmaceutical evaluation bodies and of its pharmaceutical industry are at stake, and we must all do our utmost together."⁴⁹

Many companies have set up liaison offices on Canary Wharf and several others are expected to do so shortly.⁵⁰ One major firm, the German company Bayer, has relocated its European regulatory headquarters to Canary Wharf.

In October, 1995, the first pan-European drug was approved. The drug, a fertility treatment called Gonal-F, was given a single commercial license, permitting its sale in all 15 Member States.⁵¹ Through April 1, 1997, a total of thirty-three European-wide marketing authorizations have been granted and eleven others are awaiting final approval by the Commission.⁵² Equally importantly, two-thirds of the applications received by the EMEA have not been for biotechnology products, indicating "Industry confidence in the centralized system."⁵³ Moreover, there have been 50 completed mutual recognition of national authorizations for human medicinal products, with only three arbitrations.⁵⁴

⁴⁸ "EMEA Doors Now Open for Business," Marketletter, February 6, 1995. Available on NEXIS, Europe library.

⁴⁹ Ibid.

⁵⁰ Daniel Green, "European Medicines . . ." p. 13.

⁵¹ Daniel Green, "EU-wide drugs approval begins," Financial Times October 24, 1995, p. 2.

⁵² Daniel Green, "Fast-track to Approval," Financial Times, April 24, 1997.

⁵³ EMEA Status Report, October 21, 1996.

⁵⁴ Ibid.

Compared to most other consumer products, including those with important health and safety dimensions such as food and automobiles, the EU has found it relatively difficult to create a single market for medical products.⁵⁵ Nonetheless it has now finally created a legal and institutional framework for accomplishing this goal. The EU's considerable progress in coordinating the drug approval policies among its fifteen Member States has been paralleled by progress in coordinating drug regulation policies among other developed nations, a topic to which we now turn.

III. INTERNATIONAL HARMONIZATION

Preliminary Efforts

While the EU represents the world's most ambitious effort to coordinate national pharmaceutical regulations, a number of important initiatives have been undertaken at the global level as well. Informally, pharmacopoeias (official drug manuals), especially the Nordic, European and International Pharmacopoeias, have historically played a role in creating uniform norms. These manuals allow scientists around the world to compare notes on drug descriptions, compounds, and expectations of efficacy. Often, though, they simply gave administrators from different countries the opportunity to dig in their heels by officially publishing their preferred interpretations.⁵⁶

The first formal international harmonization took place in 1973, when the Benelux countries initiated a supranational registration system. "It was perhaps this venture, more than anything else, which caused the pharmaceutical industry to argue for 'mutual recognition' of regulatory decisions,

⁵⁵ See David Vogel, Trading Up: Consumer and Environmental Regulation in a Global Economy, Cambridge: Harvard University Press, 1993, chapters 2, 3.

⁵⁶ Rosemary Kanusky, "Pharmaceutical Harmonization . . ." p. 689.

particularly in the European Community."⁵⁷ The five members of the Nordic Council, only one of which was a member of the EC, also adopted a common drug registration procedure. Although its results were non-binding, a drug approved in one state could be licensed by another without a separate testing procedure. At the international level, a 1979 conference in Rome led to a multilateral agreement to work toward creating testing and evaluation guidelines that could be shared by Council for Mutual Economic Assistance, European Free Trade Area, and Nordic Council of Medicines.⁵⁸ No concrete results developed, however, until this working group's interests began to overlap with the interests of the EC and the United States in the mid-1980s.

United States

Prior to the mid 1980s, the cooperation of the American Food and Drug Administration with its counter-parts in other nations was extremely limited. The FDA had entered into an agreement defining good manufacturing practices with Switzerland, Sweden, Canada, and Japan and had signed an agreement establishing good laboratory practices with Canada, Sweden, Switzerland, West Germany, France, Italy, the Netherlands and the United Kingdom.⁵⁹ However the U.S. required that clinical testing for all drugs, whether domestic or imported, be performed in the United States. This forced importers to duplicate costly tests and restructure trials to conform to American laboratory standards. "This policy seems to have had a significant effect in delaying the introduction of foreign-discovered drugs into the United States -- even those foreign drugs that represented significant

⁵⁷ Graham Dukes, The Effects of Drug Regulation: A Survey based on the European Studies of Drug Regulation (1985) pp. 18-19. Quoted in Rosemary Kanusky, "Pharmaceutical Harmonization . . ." p. 688.

⁵⁸ Rosemary Kanusky, "Pharmaceutical Harmonization . . ." p. 687-688.

⁵⁹ Ibid.

advances."⁶⁰

The FDA had long been criticized for the so-called "drug lag" - the length of time it took before a drug approved in a European country became available in the United States. During the mid 1980s these criticisms become political significant as AIDS activists blamed the agency for the slow rate of approval of drugs that might be effective against the AIDS virus.⁶¹ In part as a response to these pressures, the FDA adopted guidelines allowing research conducted outside the United States to be incorporated into both animal and clinical trial applications.⁶² However, the actual results of this new policy have been modest. Since the mid-1980s, the FDA has approved only five new drug applications based on foreign data alone as well as nine based on both domestic and foreign data.⁶³

In 1989, the FDA took a highly unconventional step to accommodate AIDS patients, granting a "personal use exemption" for individuals to bring a drug into the United States for their own use if it has been approved for use in another country.⁶⁴ This led to widespread growth of "buyers clubs," which import and distribute drugs, at lower prices, primarily but not limited to people with AIDS.⁶⁵ Although they provide a crucial service, these clubs have taken advantage of arbitrage opportunities by importing drugs approved by the FDA but available at a lower price abroad.⁶⁶ For example, the

⁶⁰ David Jordan, "International Regulatory Harmonization . . ." p. 490.

⁶¹ See David Vogel, "When Consumers Oppose Consumer Protection: The Politics of Regulatory Backlash," *Journal of Public Policy* October-December 1990, pp. 458-461. For data on the drug lag, see *Proposals to Reform Drug Regulation Law* Washing DC. American Enterprise Institute, 1979.

⁶² Relihan, "Expediting FDA Approval," p. 251.

⁶³ Rosemary Kanusky, "Pharmaceutical Harmonization . . ." p. 675.

⁶⁴ Eric Lindemann, "Importing AIDS Drugs . . ." p. 134, 140-142.

⁶⁵ Ibid.

⁶⁶ See Relihan, "Expediting FDA Approval," p. 232.

pneumonia drug Nebupent was marketed in the U.S. up to \$175 per vial. Buyers clubs "imported" a similar drug, Pentamide, from England and resold it in the U.S. for \$40 per vial. A German company subsequently cut the price to \$30 per vial.⁶⁷

Under increasing pressure to expedite the drug approval process, U.S. regulators became more willing to cooperate with other regulatory agencies. In 1990, the U.S. and the European Commission completed a Memorandum of Understanding which standardized good manufacturing practices and good laboratory practices between FDA and all EC Member States. The following year the United States, the EC, and Canada sponsored a conference to harmonize the names of health care products. On November 14, 1991, as part of a more comprehensive reform package, HHS Secretary Sullivan announced the FDA's intent to "harmonize" American testing standards with those of other industrialized nations. Sullivan predicted that harmonization would lead to the "development of common testing procedures [which] would reduce . . . duplication [of tests] and speed the development of drugs worldwide."⁶⁸

Four days later, the President's Council on Competitiveness sounded a variation on this theme, calling for "reciprocity agreements," or mutual recognition of drug approval which would be "negotiated on a country-by-country basis."⁶⁹ The FDA subsequently issued a report on international harmonization. It argued that harmonization offered a number of major public health benefits, including decreasing the spread of disease within countries and across borders; increasing patient access to safe and effective products; improving the quality, safety and efficacy of imported drugs; and

⁶⁷ Ibid.

⁶⁸ David Jordan "International Regulatory Harmonization: A New Era in Prescription Drug Approval, Vanderbilt Journal of Transaction Law Vol. 25 p. 492.

⁶⁹ Relihan, "Expediting FDA Approval," p. 256. See also Jordan, "International Regulatory Harmonization . . ." p. 496.

increasing information transfers between countries on public health issues.⁷⁰

The International Conference on Harmonization

The most important effort to promote the global standardization of drug approval policies and procedures has taken place through the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceutical for Human Use (ICH). ICH participants include officials from the US FDA, the EU's Committee for the Proprietary Medicinal Products (CPMP) and the Japanese Ministry of Health and Welfare as well as representatives from pharmaceutical companies in the EU, the United States and Japan. These three markets account for seventy-five percent of the world's production of medicines and ninety percent of global pharmaceutical research and development.⁷¹

The ICH grew out of a meetings between regulatory officials from Europe, the United States and Japan and the International Federation of Pharmaceutical Manufacturers Association. Its first session took place shortly after the EC Council began the process of drafting the Maastricht Treaty, since the commitment of the EC/EU to establish regional regulatory standards made it possible to seek agreement on global ones.

Over 1,000 participants attended ICH's the first conference, held in Brussels in 1991. In addition to establishing a process of negotiated rulemaking to harmonize regulatory guidelines, the conference approved a "minimum data blueprint" guideline, subsequently incorporated into U.S., EU and Japanese law.⁷² The blueprint defines data collection conditions acceptable in the three countries,

⁷⁰ Joseph Contrera, "Comment: The Food and Drug Administration and the International Conference on Harmonization: How Harmonious Will International Pharmaceutical Regulations Become?" *Administrative Law Journal* Winter, 1995, p. 930.

⁷¹ Jordan, "Prescription Drug Approval," p. 492.

⁷² *Ibid*, p. 493.

allowing a firm to file the same data package in each. While the data submitted are still evaluated by national officials--who may still demand data beyond the scope of the minimum data blueprint--this guideline eliminates the need for costly and repetitive tests. For example, before the ICH, the EU, Japan and the United States had no common control conditions for conducting laboratory tests. Now control conditions, such as the definition of "room temperature," are precisely defined.

The guideline also standardized long-term toxicity tests, limiting repeated dose toxicity studies to six months.⁷³ This should "cut industry's costs by a total of \$100 million annually -- and save the lives of 35,000 laboratory animals, itself an increasingly important consideration."⁷⁴ According to one estimate, the minimum data blueprint's elimination of duplicate testing will save up to 100,000 Ecus for every new medicinal product, while reducing long-term toxicity tests from one year to six months will save as much as 500,000 Ecus per new substance.⁷⁵

Still, the most important outcome of the 1991 Conference was political.⁷⁶ Its overriding accomplishment was that all three regulatory agencies were willing to commit publicly to harmonization principles.⁷⁷ This in turn reflected the regulators' acknowledgement that "they were all wasting a lot of money by requiring duplicate testing without contributing anything to improving health

⁷³ The previous standard, "Lethal Dose 50," would increase doses administered to laboratory animals until 50% of the animals died. Ironically, this testing phase lasted longest for drugs that had the safest toxicity levels.

⁷⁴ "A Faster Track for New Drugs," *Financial Times*, December 9, 1991, p. 20.

⁷⁵ "EC, USA and Japan Ready to Reduce Pharmaceutical Product-testing and Animal Tests Drastically," *Rapid*, Commission of the European Communities, November 13, 1991.

⁷⁶ The Pharmaceutical Business News noted that "to put all the emphasis on the conference as a scientific meeting would be to distort its impact, representing as it did the first time regulators and industry have met on such a large and public stage." [I can get this for you on nexus.] (quoted in Jordan, "Prescription Drug Approval," p. 494.)

⁷⁷ David Jordan, "International Regulatory Harmonization . . ." p. 495.

protection."⁷⁸ The FDA's participation was especially significant since, as recently as the mid-1980s, the agency had publicly regarded foreign clinical data as "too precarious" on which to base a marketing approval decision.⁷⁹

A second ICH conference was held in October 1993 in Orlando, Florida. In his keynote address to the conference's 1,600 participants, FDA Commissioner David Kessler stated that, "Science driven harmonization can curtail duplication, and thereby significantly reduce the cost of new drug development -- not just in dollars spent by the industry but in the risk taken by patients, in the experimentation with laboratory animals, and in the regulatory efforts of our governments." He added, "It has the potential for a major breakthrough in the drug approval process by making a common registration package a realistic possibility."⁸⁰ The Orlando conference agreed on common procedures for animal-based experiments to detect toxicity in reproductive systems and established common definitions and standards for clinical safety data management.⁸¹

A third session, attended by 2400 delegates from pharmaceutical firms and forty governments, took place in Japan in November, 1995. Its primary accomplishments were agreements on uniform guidelines for the clinical testing of new drugs and good clinical practice. These agreements are intended to facilitate the mutual acceptance of data on clinical trials, thus significantly reducing the costs of drug development. ICH3 also agreed on a work program to complete the development of 50 common guidelines on the steps necessary to demonstrate the safety, quality and efficacy of new

⁷⁸ Ibid, p. 495.

⁷⁹ Jordan, "Prescription Drug Approval," p. 495.

⁸⁰ Quoted in Contrera "Comment", p. 929.

⁸¹ Dan Kidd, "The International Conference on Pharmaceutical Regulations, the European Medicines Evaluation Agency, and the FDA: Who's Zooming Who?" Indiana Journal of Global Legal Studies, Fall, 1997, p. 5.

medicines. One ICH working group is working on harmonizing both the medical technology used by regulatory agencies as well as electronic data transmission standards. Agreement on the later could eventually make it possible for a company to electronically submit the same dossier or application to the FDA the EMEA and the MHW.

To date, nineteen guidelines have been formally approved by conference participants, four of which have been enacted into law in Europe, the United States and Japan.⁸² They cover reproductive toxicity in animals, clinical studies among the elderly, stability testing of new active substances, and dose/response information to support drug registration. An additional thirty-eight guidelines are currently under development. What is especially significant is that a large number of firms in the United States, Japan and Europe have already adopted the first eleven guidelines agreed to by the ICH.⁸³ According to a survey conducted by Japan's MHW, more than 90 percent of the quality guidelines developed through the ICH process are being used by companies.⁸⁴ The world's twenty-five largest firms have adopted nearly 100% of the ICH guidelines.⁸⁵

The ICH meetings have also helped improve communication and trust among regulators in different regions and fostered the establishment of more sophisticated and comprehensive mechanisms for data exchange, including an experimental effort to exchange data regarding the side-effects of

⁸² George Bermann, "Regulatory Cooperation Between the European Commission and U.S. Administrative Agencies," The Administrative Law Journal Vol. 9, 1996, p.964.

⁸³ "Impact of First ICH Guidelines," Information Access Company Newsletter Database, October 30, 1995.

⁸⁴ "FDA Challenged by its Involvement in International Harmonization Efforts," BNA Health Care Daily, Jan 19, 1996.

⁸⁵ "Euro Commission, EMEA Consider Global Dossier," IAC Industry Express June 6, 1996.

previously approved drugs though floppy disks and across the Internet.⁸⁶ They have also developed a common glossary of medical terminology.

While ICH was originally envisioned as a six-year process, a fourth conference has planned for 1997 in Belgium. Its objective will be to adopt of a number of sufficient guidelines so as to create a core dossier that would be acceptable to regulatory bodies in the United States, Europe and Japan. As the closing plenary session of the Yokohama conference, Roger Williams, associate director of the Science and Medical Affairs Center for Drug Evaluation and Research of the FDA stated: "We've just stepped up close to the realization of a dream. A dream: we can say it's a global dossier, which is available though any country in the world, or is acceptable to any regulatory authority in the world." He added: "Let's make an effort to realize this dream."⁸⁷

Originally comprised of only government and business delegations from Japan, the EU and the US, each successive meeting of the ICH has been attended by delegates from additional countries. In light of the economic importance of the triad, it is highly likely that many ICH guidelines will be adopted by many other countries as well. For its part, the World Health Organization has begun to encourage developing countries to adopt them. In brief, "ICH has been far more successful than anyone anticipated."⁸⁸

National Responses

Not surprisingly, the region which has found it the easiest to adjust to the ICH's guidelines and standards has been the EU. Most guidelines "largely overlap with current EC legislation, so the ICH guidelines do not imply any major changes in the EEC acceptance policy for pharmaceutical

⁸⁶ "Better Medicine to be Side-Effect of New Network," Nikkei Weekly May 6, 1996.

⁸⁷ "ICH - A Great Success".

⁸⁸ Jill Wechsler, "Washington vs. the world?" Pharmaceutical Executive February, 1966, p. 16.

products."⁸⁹ This is particularly true of the Good Clinical Practice guidelines. As in the case of a number of other global standards, most notably ISO 9000, the experience the Europeans gained in harmonizing regulations among the EU's Member States has both enabled and encouraged it to play a leadership role in promoting international regulatory cooperation. At the same time, the work of the ICH has itself contributed to the harmonization of drug approval standards and procedures within the Union.

Japan has experienced the most difficulty adjusting to the ICH. Of particular concern to the Japanese are racial differences that can lead to different reactions to the same dose of the same drug across populations. Japan, like other states, has been reluctant to accept foreign data as the basis for drug evaluation. This began to change in 1986 following bi-lateral negotiations with the United States. But while Japan is "increasingly willing to accept toxicity tests and preclinical data from other countries . . . it still insists on Japanese clinical data."⁹⁰ In addition, Japan's distinctive evaluation standards and criteria require considerable additional testing.⁹¹ Nobuto Nakamura, general manager of the Pharmaceutical Development Division of Takeda Chemical Industries, has expressed concern that "when it becomes possible to use Western Clinical Data in Japan based on the results of the International Conference of Harmonization, there is a risk that clinical trials [in Japan] will be reduced to a mere formality since sponsors will minimize the number of studies performed locally and transfer

⁸⁹ "EEC/US/Japan: Major Agreement on Pharmaceutical Trials," European Environment, November 26, 1991, p. III-1.

⁹⁰ "Prescription for success: The Japanese Prefer their Own Medicines," Financial Times, December 3, 1990, p. 7.

⁹¹ William Currie, "Drug Development and Registration in Japan: Threshold of Transition," Journal of Clinical Pharmacology vol. 33 (1989) pp. 100ff, explains dissimilar data requirements as cultural and political phenomena. See also Rosemary Kanusky, "Pharmaceutical Harmonization . . ." op. cit., p. 683-686.

them overseas."⁹²

However, in preparation for ICH2, the Japanese Ministry of Health and Welfare created "Pharma Dream 21," a \$10 million scheme "for the promotion of harmonization of drug regulation . . . particularly in the area of racial differences from the point of view of clinical science."⁹³ Japan has also responded to the need for harmonizing good clinical practice by increasing its number of inspectors, as Japanese monitoring has been a continuing source of complaints by US and European regulators.⁹⁴ However at the closing session of ICH3, a senior Japanese official in the Ministry of Health and Welfare stated that he was pleased that so "many guidelines in which international standards are provided for were agreed upon in order to avoid duplicating tests and wasting time and costs," and pledged to make sure that these guidelines are put into practice."⁹⁵

One of the ICH's major impacts will be to improve the quality of Japanese testing procedures, bringing them more closely into line with those of Europe and the United States. This will enable Japanese firms to use the results of tests conducted in Japan on their foreign applications. Equally importantly, it will also improve the welfare of Japanese patients by requiring the adoption of western standards of patient notification. As one observer put it:

Inherent in a standard protocol is an enforceable requirement for informed consent. Suddenly patients are empowered to request information before signing on the dotted line. Once information is shared, the previous sole holders of information [senior Japanese investigators known as "Big Bosses"] are forced off their pedestals into the real world. The psychological

⁹² "Japan Urgently Needs Better Quality Clinical Trials," Pharma Japan, March 20, 1995, available on NEXIS, world library.

⁹³ "Funding for Japan's 'Pharma Dream 21,'" Marketletter, January 20, 1992, on LEXIS, world library.

⁹⁴ "Japan: Mr. Fujii of PAB Indicates Koseisho's Strong Commitment to GCP and ICH," Pharma Japan, August 31, 1992, p. 1.

⁹⁵ "ICH - A Great Success," Daily News Biotechnology and Medical Technology, December 11, 1995.

implications in Japan are dramatic.⁹⁶

For the FDA, its participation in the ICH has complimented its ongoing efforts to speed up the approval process. Since the "drug lag" is by definition, based on the gap between the approval time of new drugs in Europe and the United States, to the extent that there is international agreement about the preclinical and clinical tests and data needed to support a new drug approval application, it is likely to steadily diminish. While mutual recognition of drug approval between the FDA and the EMEA is unlikely in the foreseeable future, a number of the EMEA's criteria for both efficacy and effectiveness as well as its requirements of clinical review and scientific vigor, are now sufficiently similar to those of the FDA so as to permit both agencies to rely more on data prepared for their counterparts.⁹⁷

The formation of the EMEA in particular and the work of the ICH in general offers the FDA a way of responding to domestic political pressures for expediting the drug approval process, without compromising its health and safety standards. Just as the work of the ICH has complimented the efforts of the EU to create a single market in pharmaceutical products, so has it complimented the movement for regulatory reform in the United States. The FDA has formed internal working groups that mirror those established by the ICH's steering committee and their recommendations have already reduced the number of overlapping requirements imposed on industry.⁹⁸ This in turn has helped expedite the drug approval process.

The international coordination of national drug approval standards have generally taken place outside the framework of trade negotiations, largely because national regulatory requirements have not

⁹⁶ P. Reed Mauer, "View from Tokyo: Big Boss Era Is Ending," Daily News Biotechnology and Medical Technology, June 24, 1996.

⁹⁷ Katz, "Europe's New Drug Procedures," p. 585-586.

⁹⁸ "FDA Challenged By its Involvement in International Harmonization Efforts," BNA Health Care Daily June 19, 1996.

discriminated against drugs developed by non-domestic firms. The relative structures of American regulatory requirements have not conferred a competitive advantage on drugs developed by American firms any more than the existence of fifteen separate drug approval standards within the EU has conferred a competitive advantage on European ones. Neither the Americans nor the Europeans have regarded each other's drug approval requirements as non-tariff barriers though the Americans have complained about the difficulties of marketing American drugs in Japan. Regulations that restrict trade in the bulk ingredients used to manufacturer pharmaceuticals products, as well as the products themselves, have emerged as a source of trade conflict between the United States and the European Union. As part of negotiations on a mutual recognition agreement to reduce regulatory barriers to trade between the US and the EU, the EU has proposed mutual recognition of plan inspections performed by each other's authorities.

These negotiations remain at an impasse. One point of contention involves how on agreement on joint manufacturing practices inspection would work.⁹⁹ The Americans want to be able to evaluate the inspection reports of EU authorities and then draw their own conclusions. For its part the EU insists that the FDA rely on the conclusions of EU inspections. The United States is also concerned about the ability of Brussels to enforce any agreement on inspection standards with the United States since each member state currently operates its own inspection process. American officials note that while the Europeans claim they support harmonization in order to "enhance trade," the Americans, the United States currently imports 80 percent of bulk ingredients for pharmaceutical manufacturers - 40 percent from Italy.

Underlying this dispute is a history of American doubts with the adequacy of foreign inspection standards. Consequently, the FDA has frequently undertaken its own on-site inspections, rather than

⁹⁹ Wechsler p. 20.

rely upon European government inspections. Between 1977 and 1991, the FDA audited sixty-six non-U.S. sites in fifteen different countries.¹⁰⁰ It found a number of shortcomings including unavailable, inadequate records, protocol nonadherence, patient consent requirements and inadequate drug accountability. These audits are both expensive and time-consuming and defeat one of the important sources and purposes of cooperation, which is precisely to enable national regulatory authorities to be able to rely upon their counter-parts in other nations.

CONCLUSION

The developments described in this paper represent part of a much broader effort on the part of governments to facilitate regional and international trade by reducing technical or nontariff barriers to trade¹⁰¹ Reducing the role of national regulations as trade barriers was a critical component of the EU's "1992" program to create a single European market. It was also a major objective of the Uruguay Round GATT negotiations, which produced a significant strengthening of various standards codes. All WTO signatories were required to accept both a Technical Barriers to Trade code which applies to product standards as well as an Agreement on Sanitary and Phytosanitary which limits the use of food and agricultural standards as trade barriers. Because both of the complexity and comprehensiveness of pharmaceutical regulations, both the regional and international coordination of drug regulation has proven especially difficult. Nonetheless, since the early 1990s, substantial progress in globalizing this area of regulation has taken place as well.

As in these other areas, these initiatives in part reflect the interests of globally oriented firms in

¹⁰⁰ Contera "Comment", p. 947.

¹⁰¹ For excellent overviews of this subject see, Alan Sykes, Product Standards for Internationally Trade Goods Markets Washington D.C. Brookings Institution, 1995, and Regulatory Co-operation for an Interdependent World Paris: OECD, 1994.

increasing their access to international markets. To the extent that an international standard for drug approval emerges, these firms will find it both easier and less expensive to develop and market products on a global basis. The result is likely to widen the gap between internationally and domestically-oriented drug firms. However, to the extent that the international harmonization of testing requirements results in a reduction in drug approval times, smaller, under-capitalized firms, such as those in the biotechnology sector, are likely to benefit as well: even a slight increase in approval time can significantly increase the net present value of a pharmaceutical product. "A one and one-half reduction in drug approval time can reduce the time necessary to recoup research and development expenditures by five years."¹⁰²

The globalization of regulation, particularly when it has taken place under the auspices of trade negotiations and agreements, has often been criticized on the grounds that it is likely to lead to a "race to the bottom."¹⁰³ According to this perspective, firms will pressure their governments to lower their standards to match those of their trading partners, lest they experience a competitive disadvantage. Yet this dynamic does not hold in the case of pharmaceutical regulation. Most obviously, regulatory authorities are not competing with one another; rather they are coordinating their regulatory standards. The EMEA's standards are not laxer than those of any of its Member States and indeed are more comprehensive than a number of them. And far from establishing minimum standards of drug regulation, the ICH's guidelines represent an effort to formulate state of the art standards.

Rather than compromising public health and safety, increasing international coordination is likely to improve it. It may enable companies to shift resources from conducting multiple tests and in

¹⁰² Dillman, "Desperate Times," p. 936.

¹⁰³ For an excellent analysis of this literature, see, Peter Swire, "The Race to Laxity and the Race to Undesirability: Explaining Failures in Competition Among Jurisdictions in Environmental Law." *Yale Law and Policy Review*, *Yale Journal of Regulation*, 1996, pp.67-110.

many case duplicate tests to increasing their research and development budgets. It will also reduce the number of both people and animals on which drugs are tested. Rather than exposing citizens to more unsafe drugs, it may well make safer drugs available to them sooner. In addition, it is likely to make it easier for the EMEA, the MHW and the FDA, as well as consumer groups in each country, to monitor each other's performance, particularly with respect to the recall of unsafe drugs. Indeed, similar testing requirements and procedures among ICH countries might lead to more care and focus, resulting in greater safety. Finally, the adoption of ICH guidelines by the world's three most important regulatory bodies is likely to both assist and encourage drug approval bodies in less developed countries to strengthen their own often inadequate standards.

With respect both to the approval of new drugs and the recall of unsafe ones. Moreover, the increase in coordination and communication among national regulatory authorities that the work of the ICH is promoting is likely to facilitate the more rapid dissemination and adopting of improved testing requirements and procedures.

A useful parallel may be made with global environmental treaties. These treaties strengthen the effectiveness of national environmental regulations since international regulatory cooperation is critical to address environmental problems which transcend national boundaries. At first glance, drug regulation appears to have little in common with ozone depletion as the former only affects the health and safety of the citizens in one country. Yet on further reflection, there is an important similarity. For in both cases, international cooperation and coordination has a critical role to play in improving the effectiveness of national regulatory standards.