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A COMPARISON OF DRUG APPROVAL AT THE FDA AND THE EMEA/CPMP

MARTINE KRAUS, PH.D.*

INTRODUCTION

This Article addresses drug approval at the Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMA), which is the European equivalent of the FDA. I will also address the Committee for Proprietary Medicinal Products (CPMP). I wish to approach this with a bit of a historical perspective.

To return to what Dr. Edward Penhoet mentioned in his article, regulation serves a role in assuring product safety and the consistency of the manufacturing process.¹ Since the 1960s, both Europe and the United States have developed very different regulatory regimes governing the testing, manufacturing, marketing and post-marketing controls of both pharmaceuticals and biologics.

In the 1970s, the FDA regulatory regime was described as being very legalistic, very complex, stringent, adversarial, and inflexible. In short, the regime was considered to be very burdensome and costly. The European regulatory regime was also described as burdensome because it was very fragmented, and you had to deal with many different countries and their protectionist policies; yet, the European regime was also informal and flexible, based on negotiated rule-making and self-regulation by the industry. As such, it was considered less burdensome and costly than the American regime.

In the 1980s, however, several developments blurred this clear distinction between the United States and Europe. Commissioner Lehman, in his

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1. Edward Penhoet, Ph.D., *Science & Technology Policy: A CEO's View*, 33 CAL. W. L. REV. 15, 27 (1996) (this volume).

article,² places much emphasis on the globalization of the pharmaceutical industry, and its effects on patent law. Globalization also affected the regulation of drugs, creating pressure for the mutual recognition of data, and the international harmonization of requirements, as illustrated by the International Conference on Harmonization (ICH).³ On the other hand, there have been many domestic initiatives to streamline and accelerate the regulatory process in the United States. In Europe, there have also been initiatives to streamline and accelerate the regulatory process, spurred by the imperative of the Single European Market.

With those influences and changes of the 1980s, we can now, in the 1990s, ask, "What differences remain between Europe and the United States that truly affect the cost of the end product?" My conclusions here are based on the regulation of biologics.

DIVERGENCE AND CONVERGENCE OF UNITED STATES AND EUROPEAN REGULATORY REGIMES IN THE 1990S: CONCLUSIONS

Regulatory divergence remains in a variety of areas in the 1990s. Although there has been progress toward centralization in the European Union, the European regime is still much more fragmented and more complex than the American regime. Furthermore, differences in regulatory styles persist with the order now being reversed: Europe is now more legalistic than the U.S. FDA and regulatory enforcement and interaction with regulators now tend to be more informal in the United States than in Europe.

As to regulatory approaches and requirements, we still see substantial differences in agency approaches and the directly related requirements. The FDA continues to place its focus on the manufacturing facilities—much more so than do the European authorities. The European Union instead places its focus on process control analysis. Review times for product approval are shorter in Europe than in the United States, especially if we compare the CPMP, the main approval committee of the European Commission, to the FDA without considering subsequent marketing authorizations granted by the member states. On the other hand, the United States is more expedient in approving category 1 and 2 process changes.⁴

In spite of these areas of divergence, there are also some areas of convergence. One important dimension of convergence is stringency. Stringency of safety and efficacy standards is no longer a characteristic of the FDA alone. Both the current European and United States systems are subject

2. See generally, Bruce Lehman, *Major Biotechnology Issues for the U.S. Patent and Trademark Office*, 33 CAL. W. L. REV. 49 (1996) (this volume).

3. C.S. Kumkumian, *International Council for Harmonization Stability Guidelines: Food and Drug Administration Regulatory Perspective*, 28 DRUG INF. J. 635 (1994).

4. 21 C.F.R. § 558.3 (1996). Category 1 consists of minor process changes such as the establishment of a manufacturer's cell bank. Category 2 includes more important process changes such as the installment of new fermenter equipment.

to over-regulation and provide very few incentives for the regulator not to err on the side of caution.

Convergence is also occurring in the area of review times. The European Union and the United States product approval times are converging as shown by a recent study published by the FDA in December 1995.⁵ The study is based on data from the 1990s, but changes in review times have really been triggered by the 1992 Prescription Drug User Fee Act.⁶

Thirdly, with the recent issuance of a European Union Directive on "process variations," (which is the European equivalent of a process change), the convergence of review times for process changes can be expected.

Fourthly, Greg Simon addresses the elimination of the Establishment License Application (ELA) for well-characterized biotechnology products.⁷ While the FDA is moving away from its focus on manufacturing facilities, the European Union has introduced a Site Master File, which is an abbreviated version of an establishment license application. European authorities have also increased the number of inspections of manufacturing facilities—including inspections of American facilities, which illustrates an increased focus on manufacturing facilities by the Europeans.

Finally, the European Union has recently issued community-wide guidelines on clinical trials that attempt to harmonize requirements between European countries. With the ICH leading the way, we will also see an increased international harmonization in this area. We will see fewer and fewer American companies going to Europe to carry out their Phase I clinical trials,⁸ which in the 1980s was very common.

CASE STUDY OF A MULTI-NATIONAL CORPORATION

I would like to illustrate my comments with an example of a particular company, whose name I will not reveal. This company is a multi-national pharmaceutical company that has developed and manufactures its product, a biotechnology-derived biologic, in the United States but sought approval for the product in both Europe and the United States. Before commenting on the approval process for the product of this particular company, I would like to quote the company's director of regulatory affairs. The company's regulatory affairs official said, "We got the approval in the U.S. and we thought: If we can get it approved in the U.S., we can get it approved

5. U.S. FOOD AND DRUG ADMINISTRATION, *TIMELY ACCESS TO NEW DRUGS IN THE 1990S: AN INTERNATIONAL COMPARISON*, Dec. 1995.

6. Alicia A. Barnett, *The State of Health Care in America in 1995*, BUSINESS AND HEALTH, Jan. 1995, at 41. The Act calls for the agency to take action on most new drug applications within 12 months. User fees collected from the industry now also allow the FDA's review office to increase staffing levels and, hence, the pace of drug review.

7. Greg Simon, *FDA Reform: The White House View*, 33 CAL. W. L. REV. 109, 110-111 (1996) (this volume).

8. 32 C.F.R. §312.21 (1996). Phase I trials in humans are small pilot studies designed to determine the drug's therapeutic dose range and detect adverse effects in relation to effectiveness.

everywhere. The U.S. has the highest standard. That was a great mistake.”

The company had submitted its application to the FDA and gained approval after a lengthy review process. It then submitted the same application to the European authorities by way of a “rapporteur country.”⁹ After a few months, the company received the news that its submission was unacceptable, that it was not going to be considered for review, and that the company needed to submit an entirely new application. The company took a year to recover from the rejection, another year to prepare its new dossier, and then, finally, went through the European approval process fairly quickly.

The number of hurdles that the company had to face in Europe reflects a much more complex system than is the case in the United States. This is shown in Figure 1. The company submitted its dossier to the rapporteur country, which reviewed the dossier and made an assessment report that circulated to all member states. The dossier then moved on to the CPMP and the Biotechnology Working Party,¹⁰ where the company defended parts of its dossier and responded to remaining questions before gaining approval. After gaining approval from the CPMP, the company still needed to gain marketing approval from all member states individually in order to be able to sell its product in all countries in the European Union. In addition, the company’s U.S. manufacturing facilities were also inspected by the British authorities.¹¹

The company gained approval according to the so-called “concertation procedure,” which was in place until very recently. We now also have in place the European Union “centralized procedure.” Both procedures are very complex in comparison to the FDA. The far right of Figure 1 shows a procedure that many are familiar with: the FDA approval process. In the U.S., the company’s dossier went to the Center for Biological Evaluation and Research (CBER), and then circulated to several reviewers who specialize by discipline and section of the application (toxicology, statistics, clinical, etc.). The company’s application was evaluated by an FDA advisory committee; the agency then carried out a site inspection, and approval was granted. As you can see, the European Union represents a much more complex system. If you look at the center part of Figure 1, while simplifying the procedure as you will no longer need marketing authorization by individual member states following approval by the CPMP, it is still a very complex system.

9. C. Parkinson & C.E. Lumley, *What can be Learned from Experience Gained Using the Old European Concertation Procedure?*, 30 DRUG INF. J. 441 (1996). The rapporteur country, is according to the so-called “concertation procedure,” the country that represents the company in front of the other member states of the European Community as well as the CPMP.

10. Working parties are composed of representatives from member states and are technology or therapeutic area specific.

11. In the future, there will continue to be a member state review, but instead of having it after approval by the CPMP, it will be part of the regulatory process. On the other hand, a company will need to negotiate with individual member states. A company may negotiate a price very fast in certain countries, such as Luxembourg, while other countries may be more reluctant to substantially reimburse expensive products. So, the company will continue to have national hurdles to overcome, but they will not be directly tied to product approval and acceptance of the dossier.

Figure 1

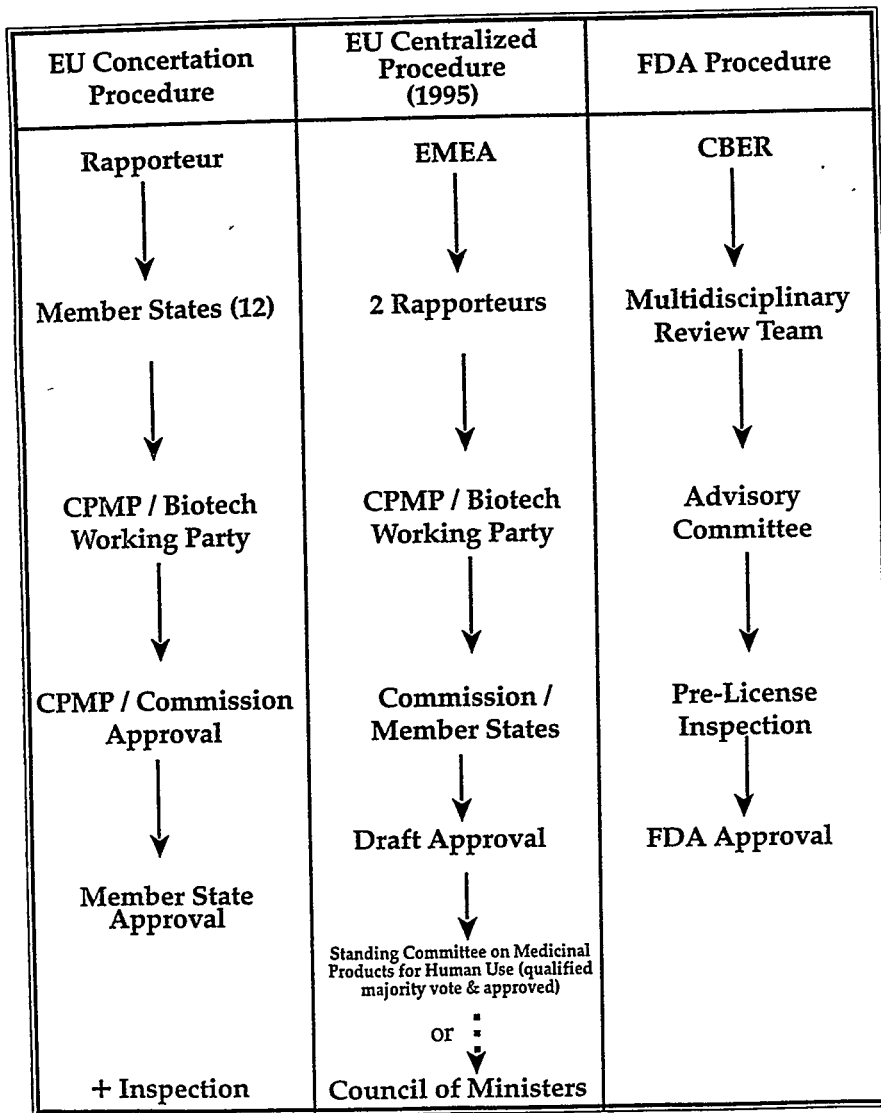
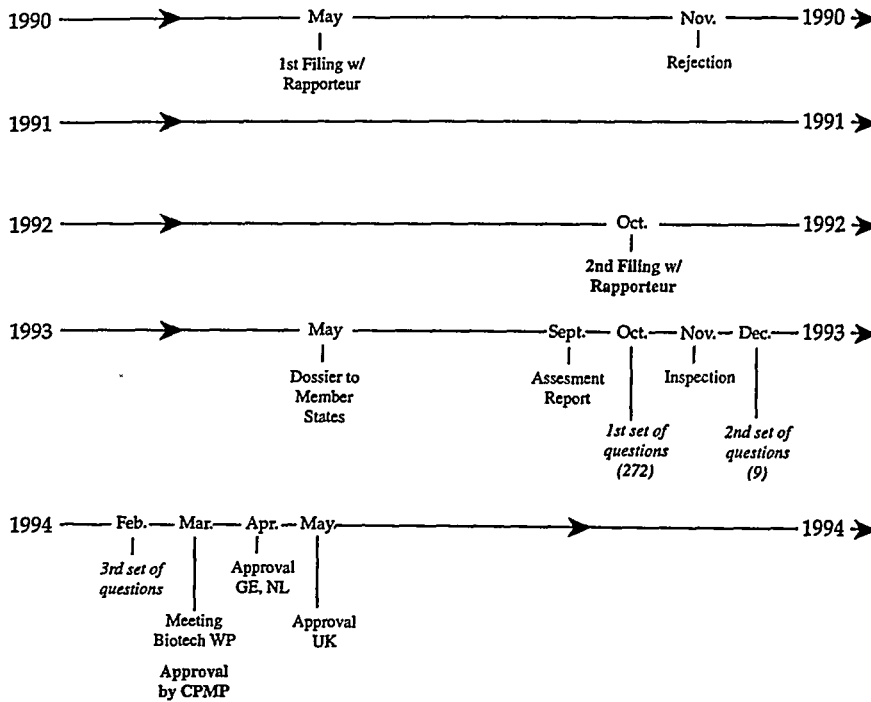


Figure 2

CPMP PROCESSING TIME FOR PRODUCT X



CPMP Approval:	18 months (following 2nd filing)
GE/NL Approval:	19 months
UK Approval:	20 months
IT Approval:	36 months
BL Approval:	still pending

Ironically, in spite of the system being more complex, it was faster for this particular company.

If you take Figure 2, regarding approval times, the company submitted its application in October of 1992. That was the second filing; the first filing had been considered unacceptable for review. The review progressed fairly quickly through the next year, 1993, to a first, second, and then third set of questions from the member states, the rapporteur country, and the Biotechnology Working Party in order to move on to product approval at the CPMP. Subsequently, the company needed approval from the individual member states, where substantial differences did arise in comparison to the United States. While the company gained its approval in 18 months from the CPMP, it took 20 months to gain approval in the United Kingdom, and 36 months in Italy—and the company is still waiting for approval in Belgium.

National differences in approval times following approval by the CPMP is definitely a problem, making it difficult to talk about differences between the FDA and the European system. In one way, approval can be faster, 18 months in Europe versus, as we will see in Figure 3, 31 months in the United States; but on the other hand, you have all these extra months while the company awaits approval from individual members states. As I mentioned earlier, the centralized procedure is meant to do away with that problem.

The FDA review time for the product was much longer. Overall, the process took 41 months, though we should subtract 10 months because of a manufacturing problems—thus, a 31 month approval process. The company submitted its application in 1989 and, for nearly a year, did not hear from the regulator. The company then received a first set of questions, a second set of questions, and a year later, a third, fourth, and fifth set of questions. The company received a lot of small sets of questions in the U.S. in a much more disorganized manner than it did in Europe, where all the questions were centralized by the rapporteur country. Eventually, approval was granted by the end of February of 1993, after a total review time of 31 months in the U.S. versus a total time 17-18 months in Europe.

On the other hand, process change reviews are much faster in the U.S. than in Europe. Category 1 and 2 process changes in particular (see Figure 4) are much faster in the United States. In the first case, U.S. authorization only requires a notification, while the European submission and review process takes a total of 90 days. In the second case, submission and review is a 30 day process in the U.S. that may easily become a 90 day process in Europe.

What is the cost of these delays? There are opportunity costs and a loss in market share. So if the company has, as in this case, a European Union market of 120 million units per year, and a United States market of the same size at \$.80/unit, the cost of a category 1, type 1 process change in the United States was \$8 million in 1995 versus \$32 million in the European Union. If we project this, and talk about a three-fold increase of the market for the year 2000, the same process change is going to cost \$24 million in the United States and \$96 million in the European Union.

These figures depend on the condition that the FDA and the European Union keep their current systems in place which, however, will not necessarily be the case. As a matter of fact, the same company recently experienced a case where, following a reviewer turnover at the FDA that left the new reviewers without any knowledge about the company's manufacturing process, the European reviewers, more familiar with the company, were able to act faster on process changes than the American reviewers. The FDA has a high rate of reviewer turnover, which is very detrimental to the agency. Thus, what is a positive characteristic of the agency, *i.e.*, its fast process change review, may be undermined by a high level of reviewer turnover within the agency.

To illustrate the cost of delays in approval, a 6 month delay in this particular case, cost the company \$48 million. Comparing the CPMP to the FDA, the 14 month delay cost the company \$112 million. That is surely not insignificant for a small biotech company, or even for a larger pharmaceutical company. As Everett Dirksen¹² said, "a million here, a million there, very soon we're talking about real money."

As to the differences in requirements and approaches, the company submitted a Product License Application (PLA) and an Establishment License Application to the United States authorities, and a Marketing Authorization Application (MAA) to the European authorities.

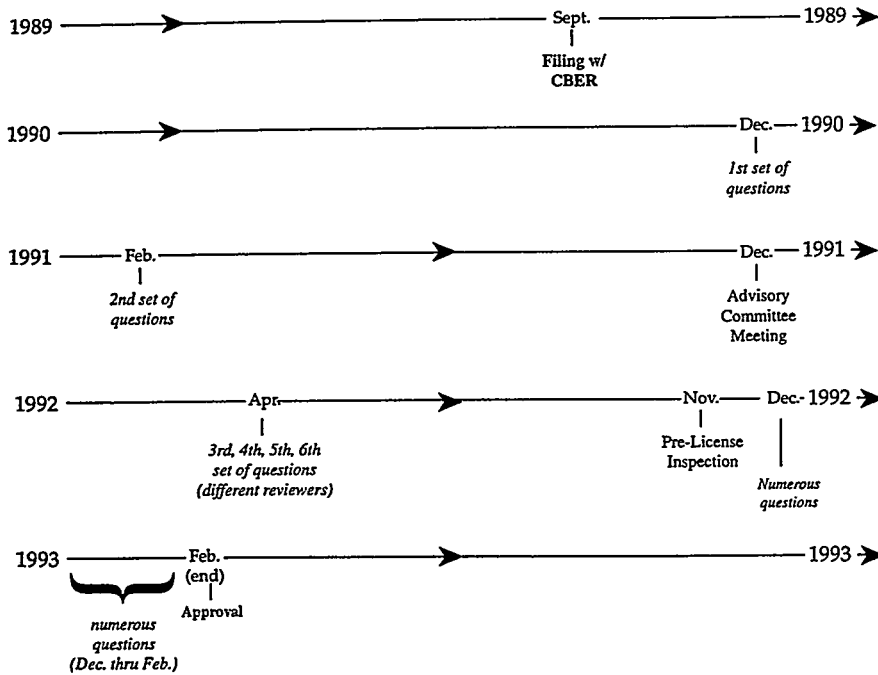
The preclinical and clinical data for the two submissions were identical. There were substantial differences, however, in the types and amount of data required by the European Union to describe the manufacturing process. By "substantial," I mean 18 volumes versus two volumes! These extra 16 volumes consisted of in process measurements proving that the company tightly controlled its manufacturing process and that the process was consistent. The U.S. focus was instead on the manufacturing facilities and equipment. In essence, the U.S. regulator would say, "Tell me how you run your operations on a daily basis and what operations you have in place to monitor the consistency of the process including details regarding the utilities, equipment, facilities, and procedures for testing the product that you are manufacturing." The European regulator instead would ask, "Tell me why you design the process the way you do and justify it. Which parameters are critical and how you control those parameters to ensure the consistency of the product?"

The company was not prepared for these differences. First, it took time to understand what the European regulators really wanted, and second, how to translate this into valid data to be provided to the European authorities. In the end, the company found itself generating a new set of data for the European application, including new specifications and standard operating procedures that emphasized consistent operation and control of the manufacturing process.

12. (R-III.) U.S. Senate majority leader in the 1960s.

Figure 3

FDA PROCESSING TIME FOR PRODUCT X



FDA Approval: 31 months (41 months - 10 bec. hold)

Figure 4

Process Change Review Times

Type of Change	US	EU
New Manufacturer's Working Cell Bank (MWCB)	<i>Category I</i> notification	<i>Type 1</i> 90 days (30 day circulation 30 day review 30 day approval)
New Fermenter Equipment	<i>Category II</i> 30 days following notification	NO
New Fermenter Scale	<i>Category III</i> 6 months	<i>Type III</i> 5 months (30 day circulation 90 day review 30 day approval)

CONCLUSION

This particular company had to learn about international submissions the hard way and I am happy to share the lesson they learned. First, you have to approach registration with an international focus. Second, you have to be current on standards that are being applied worldwide. Third, you have to be proactive and establish company standards based on those standards and/or solidly based in science or proving equivalence to those standards. Fourth, you then have to establish a core document according to all known requirements followed by special formats for each market. Most importantly, you have to devote resources to regulatory affairs at an early stage of product development. As this is often very difficult for companies with limited resources, (*i.e.*, the majority of the biotech industry) regulatory authorities should make a special effort to assist the industry in clarifying and meeting the requirements.

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