Authorisation and Withdrawal of Pharmaceutical Innovations in the European Union and in the United States (1995-2003)

Laura Cabiedes (University of Oviedo, Spain)

Summary

This is a comparative study of the average and median approval times for pharmaceutical innovations (new molecular entities -NMES- and new biologics), authorised in the United States (US) and in the European Union (EU) under the centralised procedure, during the period 1995 to 2003. Marketing withdrawals for safety reasons have been monitored, since in both cases the objective is to obtain faster reviews without compromising safety. A total of 346 innovations were authorised during this period in the US (274 NMEs and 72 new biologics) and 169 in the EU. On average for the period under study, the mean approval time for these innovations was 14.7 months in the EU versus 18.2 months in the US (16.2 months if new biologics are excluded). Similar results were obtained from the comparison of median approval times. Nevertheless, in both cases, the approval time for priority NMEs authorised by the FDA was markedly shorter. Despite the differences between both approval procedures, the percentages of withdrawals were very similar: 2.2 % in the US and between 1.6 % and 2.7 % in the EU, depending on the approach used for calculations. Finally, a comparison was also made of approval times of the 117 innovations that were authorised simultaneously in both the US and in the EU during the period under study. The results obtained in this regard differ from the previously stated ones. Although the mean approval time for standard innovations continues to be shorter in the EU, the mean approval time for pharmaceutical innovations as a whole is now shorter in the US (12.5 months versus 14.3 months in the EU). The explanation can be found in the

predominance of priority NMEs included in the set of innovations approved for both markets. This outcome reveals one of the main differences between both authorisation procedures: unlike the US, the EU has not established a fast-track review system for therapeutically relevant drugs.

1. Introduction

The aim of this study is to compare approval and review times for pharmaceutical innovations authorised by the US Food and Drug Administration (FDA) and by the European Agency for the Evaluation of Medicinal Products (EMEA), under the centralised procedure. This paper contemplates NMEs[1] and new biologics for human use authorised during the period 1995-2003. A comparison of safety-based NME withdrawals by both Agencies has also been carried out. Given that the products authorised by both Agencies are not necessarily the same, the study has identified the pharmaceutical innovations authorised simultaneously in the EU and in the US during the time period previously mentioned. This approach enabled a comparison to be made of the total approval times it took both Agencies to authorise the exact same products.

Drug approval procedures in the EU and the US underwent significant changes during the 60s and again during the 90s, until they were established as they currently stand. Among the reasons for these modifications, technical progress in the pharmaceutical sector, human tragedies resulting from drug safety issues, and delays in gaining approval for therapeutic innovations can be cited. Approval delays for new drugs that represent significant therapeutic advances have significant implications for

[1] New molecular entities, that is, drugs whose active substances have not been previously approved for therapeutic use.

both human health and returns on the R&D investments made by the industry to obtain them. One of the enormous challenges the regulatory Agencies are confronted with when approving drugs has to do with smoothing the way for patient access to drugs which represent therapeutic advances without jeopardising safety. Therein lies the interest of the study presented in this paper. Section 2 presents a brief analysis of the historical evolution of marketing authorisation procedures in the EU and in the US from the 1960s to the present time. Section 3 explains the sources of information used and the method applied for the comparative study. Section 4 covers the outcomes and finally, Section 5 presents the conclusions.

2. Historical Evolution of Marketing Authorisation Procedures in the European Union and in the United States

The pharmaceutical industry is subject to extensive regulation because of the complex nature of drugs. Authorisation procedures in particular must respond to the need to protect public health. The technical evolution the sector underwent at the beginning of the twentieth century led to the obtention of potent remedies by means of chemical synthesis. Subsequently, pharmacists began to question their responsibility with respect to the new mass-produced drugs obtained by the industry [1]. Unfortunately, time and human tragedies have been needed for approval procedures for mass-produced drugs to be founded on scientifically defined quality, safety, and efficacy criteria, as is currently the case in most developed countries.

As a consequence of the malformations caused by Thalidomide, the EU established that as of 1965 all medicinal products would require authorisation prior to marketing. Market authorisation would be granted on the basis of quality, safety, and efficacy criteria. Thalidomide was not marketed in the US, but the company provided it to more than 1,200 physicians for clinical testing [2]. Despite the fact that the Thalidomide tragedy was safety-related and not efficacy-related, the Kefauver-Harris Amendments to the Food and Drug Act in 1962 added an efficacy requirement to the existing safety parameters [3]. Thus, from the mid 1960s onwards, quality, efficacy, and safety have determined the obtention of drug marketing authorisation in the US as well as in the EU.

Shortly thereafter, criticisms arose in the US about the delays in marketing therapeutically relevant drugs and the phrase "drug lag" was coined. Later on, AIDS contributed to intensifying the drug lag controversy [3]. In Europe during the 1980s, the pharmaceutical industry pressed for faster drug approvals in the United Kingdom, Germany, and Sweden. "The first stage in imputing slowness and inefficiency to regulatory authorities was to claim that new drugs were not being approved fast enough". In particular, the Association of the British Pharmaceutical Industry claimed that "… delaying approvals was detrimental to the British economy because it resulted in drug development work going abroad" [4]. From the industry's perspective, shorter approval times for new drugs save time and expense, increase the effective life of drug patents, hence, enhancing the expected returns on R&D activities. The challenge faced by the regulatory agencies charged with approving drugs is to expedite patient access to drugs that represent therapeutic advances without compromising safety. In this context,

it is worth highlighting that therapeutic harms are (politically) more conspicuous than potential forgone therapeutic benefits [2].

In the US, "… in response to criticism that the FDA was taking too long to approve the NDAs [New Drug Applications] of drugs with potentially large therapeutic impacts, the FDA implemented a drug-classification system" in 1974 [2]. The "ABC system" sought to focus greater attention and invest more effort into A-1 drugs; that is, NMEs (classified as 1) that appear to offer significant therapeutic advance (classified as A) [5]. J. Richard Crout, who at that time was the Director of the FDA's Bureau of Drugs, preferred to call it a priority review system, as opposed to a fast track system, "… because somebody's going to look at the data and say, 'well, you … can't make the A and B drugs go faster', which [was]… true" [5].

The *Prescription Drug User Fee Act* (PDUFA) negotiated by Congress, the FDA, and the pharmaceutical industry, was passed in 1992. Under the provisions of the PDUFA, "… drug companies pay fees that allow the FDA to add more resources and speed up drug review time" [6]. Review-time goals were established that distinguished between priority drugs and standard drugs.[2] The PDUFA was passed two more times, once in 1997 and again, in 2002. Briefly put, the review-time goals established at the end of PDUFA I, II, and III were: review of 90% of priority original new drug and biologic applications within 6 months, review of 90% of standard applications within 12 months under PDUFA I, and within 10 months under PDUFA II and III [7].

[2] Priority drugs are products that appear to represent a significant therapeutic or public health advance over available therapy. Standard drugs are those not designated as priority drugs and that appear to have similar therapeutic qualities as those of an already marketed drug.

In the EU, the intense regulation of the pharmaceutical sector responds basically to two objectives: to protect public health and to complete the single market for pharmaceuticals [8]. Consequently, starting in 1978, efforts were made so that, having received authorisation in one member State, other Member States could recognise the original evaluation process. This was known as the "multi-State procedure", subject to specific deadlines. The purpose was to facilitate the authorisation of a drug in several Member States simultaneously. The results obtained with this procedure were not very positive, particularly because the decision lied ultimately with the national health care authorities and, often, dissimilar decisions were adopted with respect to the same product. Paralelly, in 1987, a concertation procedure was established for the authorisation of medicinal products resulting from biotechnical processes. The advantage of this procedure was that it minimised discrepancies between health care authorities of the different Member States.

Council Regulation (EEC) No. 2309/93,[3] in force since 1995, established new marketing authorisation procedures in the EU[4]. On the one hand, it created a new mutual recognition procedure, aimed at extending an authorisation granted in one Member State to the remaining Member States. The decision adopted according to this procedure must be a single, binding decision throughout the entire EU. Secondly, the afore-cited regulation created a centralised procedure. The centralised procedure is mandatory for high-technology products (i.e., developed by recombinant DNA

[3] Council Regulation (EEC) of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products, *Official Journal of the European Union*, L214, 24.8.1993.

[4] The reform of these procedures will come into force as of 20 November 2005, by virtue of Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004, laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, *Offcial Journal of the European Union*, L136, 30.4. 2004.

technology), and optional for other innovations (namely NMEs and medicinal products presented for new indications or administered by means of new drug delivery systems which are of significant therapeutic interest) included in List A and List B product categories, respectively. Authorisation of a drug under the centralised procedure means that the authorisation is valid in all EU Member States. The review-time goal established in the centralised procedure is 300 days under normal circumstances (210 days for scientific assessment and opinion and approximately 90 days for the decision-making process).

The EMEA was created in 1995[5]; "… partly in response to demands from consumers' organisations… and the European Parliament. It was founded to enable Community institutions to discharge their considerable responsibilities resulting from the introduction of … new marketing authorisation procedures", mainly the centralised procedure [8].

The FDA and the EMEA authorisation procedures differ in two important aspects. First, marketing authorisations granted under the centralised European procedure are subject to renewal after five years. Second, unlike the US, a fast-track initiative has not been established in the EU, though some products can receive conditional authorisation under "exceptional circumstances". All in all, the EU does not distinguish between priority-review and standard-review drugs.

[5] The EMEA has its headquarters in London and has been recently renamed the European Medicines Agency.

3. Materials and Method

The information used regarding the pharmaceutical innovations authorised in the EU under the centralised procedure was obtained from the List of Authorised Products (EPARs; European Public Assessment Reports), available at the EMEA Website http://www.emea.eu.int/). Given that not only NMEs are approved by means of the centralised procedure, a data cleaning process has been carried out, so as to eliminate duplicates and to make the comparison with innovations authorised by the FDA feasible. Furthermore, the EMEA does not distinguish between NMEs and new biologics. Although the dividing line between both is not entirely clear, most new biologics are included in List A. The estimates of approval and review times were made (except for in the last part of the study) differentiating between the two product categories establisehd by the EMEA, that is, List A and List B. The estimated approval time starts at the date of application validation to the date the European Commission makes its decision. The review time was calculated by subtracting the clock-stop time it takes sponsoring companies to respond to queries or to address deficiencies identified from the approval time. The times corresponding to withdrawn innovations have not been taken into account in the time estimates because once the European Commission adopts the decision to withdraw a marketing authorisation, the corresponding report is pulled from the EMEA website.

Much of the information about NMEs authorised by the FDA was taken from the information the FDA makes available at http://www.fda.gov/, distinguishing between priority and standard NMEs. The CDER (Center for Drug Evaluation and Research) annual reports entitled, *CDER Report to the Nation* (http://www.fda.gov/cder/reports/) have been particularly useful. Likewise, information compiled by the PhRMA

(Pharmaceutical Research and Manufacturers of America, available at http://www.phrma.org/) has also been used. Information compiled by the PhRMA has been needed to complement the FDA data for two reasons. First of all, in order to estimate mean times, since the FDA provides information dealing predominantly with median times; that is, the value that falls in the middle of the group after the numbers are ranked. According to the CDER in its reports, the median "...provides a truer picture of performance than average time, which can be unduly influenced by a few extremely long or short times".[6] Secondly, information compiled by the PhRMA on new biologics has been used. New biologic products are authorised by a separate division of the FDA, the CBER (Center for Biologics Evaluation and Research) and the corresponding information currently lacks the accuracy and comprehensiveness of data regarding NMEs. Hence, all data on new biologics authorised in the US used in this study have been obtained from PhRMA, who in turn, has obtained them from government and industry sources.

The estimated approval time, as defined by the FDA, refers to "... the time from first NDA submission to NDA approval. It includes the sum of: FDA review time for the first submission of an NDA to the Agency, plus any subsequent time during which a pharmaceutical sponsor addresses deficiencies in the NDA and resubmits the application, plus subsequent FDA review time". The review time (the time it takes the FDA to review a NDA) is the approval time minus the time taken by sponsoring companies to address deficiencies identified by the Agency.[7]

[6] A guide addressing this issue is available at http://www.fda.gov/cder/present/MedianAPtime/index.htm.

[7] See http://www.fda.gov/cder/report/reviewtimes/default.htm.

Given that marketing authorisation withdrawals in the EU under the centralised procedure imply the removal of the product from the EMEA website, the EMEA database only provides reports on favourable decisions. Therefore, to estimate the percentage of innovations withdrawn from the total innovations authorised, withdrawals were added to the denominator. The analysis of innovation withdrawals in the case of the US has been limited to NMEs, since there is no systematic, comprehensive official information available regarding biologics.[8]

4. Results

Table 1 represents the comparison of mean NME and new biologic authorisation times taken by the EMEA and the FDA during the period 1995-2003. Table 2 records the comparison of median authorisation times for the same innovations. The FDA review times are only reflected in this last table.[9] It must be emphasized that all approvals granted in 1995 under the centralised procedure come from applications initiated under the former concertation procedure from which they were transferred to the new centralised procedure. In these cases, the EMEA data base records the application validation date as 1 January 1995, resulting in underestimated times. The same applies to 8 of the 19 innovations authorised in 1996. Consequently, for these two years, the actual amount of time dedicated to processing the dossiers was also estimated. These estimates are represented by the figures in parentheses in Tables 1 and 2 for these

[8] The information provided in this regard is accompanied by the following note: "The information in this listing reflects CBER's best efforts to communicate information that has been reported to FDA. Its accuracy and comprehensiveness cannot be guaranteed", http://www.fda.gov/cber/recalls/. See also Recalls and Withdrawals at http://www.fda.gov/cber/recallsmore.htm.

[9] Provided by the FDA. As regards average times, PhRMA provides the information needed to calculate mean approval times, but not mean review times.

two years. Nevertheless, it is very likely that the figures obtained in this way are higher than the figures that would have been obtained in normal circumstances.That is, the transition process itself from the old to the new system means that the years 1995 and 1996 are not representative in principle. Hence, in the last line of Table 1, the average figure for the entire period has been calculated omitting the 11 products involved.

During the period 1995-2003, 169 pharmaceutical innovations were authorised in the EU under the centalised procedure – 63 included in List A and 106 in List B (Table 1). Given that the centralised procedure is optional for innovations included in List B, this proportion reflects its success, particularly if we take into account the fact that when a product is denied authorisation, it cannot be marketed in any EU country. It therefore appears that the pharmaceutical companies have considered that the advantages of submitting a single application rather than fifteen outweight the risk of having the authorisation denied. In the US, the number of innovations approved totalled 346: 72 new biologics and 274 NMEs (172 standard NMEs and 102 priority NMEs) (Table 1).

As shown in Table 1, the mean approval time of pharmaceutical innovations was only lower in the US versus the EU in 1998 and 1999. Approval times decreased considerably in the US in these two years, although starting in the 2000, the times observed were similar to those seen at the beginning of the period, with the exception of priority NMEs approval times. The difference compared to the EU increased substantially as of 2002. Overall, for the period 1995-2003, the average approval time for pharmaceutical innovations in the EU was 14.7 months versus 18.2 months in the US. Please note that this result remains unaltered when the comparison is made omitting

the 11 products for which the approval process began under the terms of the former EU concertation procedure, given that the figures obtained in this case are practically identical.

The gap between the EU and the US would certainly be narrower if new biologics were eliminated from the analysis, since approval times for these products are considerably greater in the US than NME approval times (26.0 months and 16.2 months, respectively). *Grosso modo*, this perspective can be approximated by comparing NME approval times in the US with approval times for List B products in the EU, since List A is largely made up of new biologics. Thus, if we apply this approach, the 3.5 month difference would decrease to 1.8 months. Likewise, with the exception of the year 1996, it is of interest to note that the mean approval time for priority NMEs authorised by the FDA was shorter for each year than it was for products included in both List A and List B of the EU.

It was only possible to calculate the mean clock-stop time for approvals granted by the EMEA. The overall mean for List A products was approximately one month greater than for List B products for the period under study. An even greater difference was obtained in a study carried out for the period 1995-1998 and appears to suggest "... that the issues addressed by the companies during this time were of a more complex nature for List A products" [9]. Given that the review time is practically the same in both cases, the key to understanding the longer approval times for high-tech products lies in the clock-stop times. On average, the mean clock-stop time for approvals during the entire study period was 4.8 months versus the review time, which amounted to 9.9

months (Table 1). With this result in hand, we can state that the target of 300 days established in the centralised procedure has been met.

Table 2 presents the estimated median times. At first glance, the clock-stop time tends to be shorter in the US than in the EU, since the difference between approval and review time is smaller in the first case. The striking exception to this is the standard NMEs in 2003, with a median value of 23.1 months and 13.8 months, respectively (Table 2). The median approval time increased significantly in both the US and in the EU between the years 1999 and 2000, albeit said increase was greater in the US. The following factors may serve as possible explanations for this trend: overworked FDA staff, growing pressure triggered by recalls of several major drugs, the greater presence of drugs targeting novel mechanisms of action [10], and the increased number of applications with multiple or prolonged review cycles.[10] Indeed, this last factor appears to account for the large gap between median approval and review times in 2000 and in 2003 for standard NMEs (4.5 and 9.3 months, respectively), reflecting the longer time taken by sponsoring companies to address deficiencies.

In turn, the long median approval and review times for priority NMEs for the year 2002 are noteworthy. According to the *CDER Report to the Nation 2003*, this was caused "... by the approval of a number of older applications coupled with a decrease in the number of new applications received".[11] With the exception of the year 2002, the review-time goals put forth in PDUFA I, I, and III have been met for priority NMEs. In

[10] See http://www.fda.gov/cder/reports/reviewtimes/default.htm.

[11] See http://www.fda.gov/cder/reports/rtn/2003/rtn2003-1.HTM.

contrast, the same connot be said of standard NMEs, at least not as regards median times, that is, after omitting the influence of extreme values.

Both the FDA and the EMEA seek faster reviews without compromising safety. Given the importance of both objectives, Table 3 shows a follow-up of marketing authorisation withdrawals due to safety reasons. To estimate the percentage of innovation withdrawals of total authorisations in the EU, apart from the 4 NMEs withdrawn shown on Table 3, another 9 innovations have had to be added to the denominator. These 9 innovationes were, in principle, voluntarily pulled out by the companies, and not due to explicit safety reasons.[12] When calculated in this way, a 2.2% innovation withdrawal rate was obtained for the period 1995-2003 (4 out of 182). If we exclude Tolcapone from the numerator, the result would be 1.6% (3 out of 182); however it must be remembered that Tolcapone was reincorporated into the market in 2004, after the study period. In the US, 2.2% of the NMEs approved were pulled off the market (6 out 274 NMEs, given that Alosetron was reintroduced into the market during the period under study). Hence, it seems that the percentage of withdrawals is very similar for approvals granted in the EU under the centralised procedure and in the US. Nevertheless, of the 9 products that were voluntarily pulled by the sponsoring company in the EU, one product withdrawal is suspected to be closely related to safety issues. The case in point is the Rotavirus Vaccine, which was approved in 1999 and withdrawn (at the sponsor's request) in 2001. It never reached the EU market.[13] The company pulled this vaccine in the US in 1999 due to a possible association between its use and

[12] These are marketing authorisation withdrawals at the sponsoring companies' request, generally alleging marketing reasons, such as the lack of sufficient market. On ocassions, the product withdrawal responds to the company not renewing the authorisation 5 years after its first application.

[13] See Withdrawal of Marketing Authorisation for the Medicinal Product "… Rotavirus Vaccine" EU/1/99/105/001. London, 7 June 2001. Doc. Ref.: EMEA/13002/01. Available at http://www.emea.eu.int/htms/human/withdraw/withdraw.htm.

the development of intussusception. If this case in point is considered a withdrawal for safety reasons, the percentage of withdrawals for safety issues in the EU would total 2.7 % (5 out of 182).

Given that the previous analysis has taken into account the pharmaceutical innovations authorised by the EMEA and by the FDA with no further restrictions, the comparative analysis carried out thus far may include different products. Therefore, Table 4 presents a comparison of the mean approval times for pharmaceutical innovations (NMEs and new biologics) simultaneously authorised in the US and in the EU (under the centralised procedure) during the period 1995-2003; that is, the times involved for the exact same products. A total of 117 innovations were simultaneously approved by both Agencies during the period under study. Of them, 84 were NMEs and 33, new biologics. It is worth noting that of the 169 innovations approved under the centralised procedure, close to 70% was approved by the FDA during the same period. This reflects a high degree of coincidence, not only with respect to the products themselves, but also in terms of the time dimension. Given this coincidence, the FDA drug classification based on therapeutic relevance has been adopted, in order to compare priority versus standard drugs in both markets. The seven NMEs that began under the provisions of the former EU concertation procedure have been omitted to avoid distorting the comparison.

The results obtained differ with respect to those previously presented in Tables 1 and 2. As shown in Table 4, the average approval time is now longer in the EU than in the US. The reason for this is found in the predominance of priority-review drugs in the set of products contemplated in this case -more than 57.0% of those that were able to be

classified. Hence the mean approval time for innovations in the EU was 14.3 months versus 12.5 months in the US. Only standard drugs obtained shorter mean approval times in the EU (14.2 months versus 17.7 months in the US).

It is remarkable that in the EU there is hardly any difference between mean approval times for priority and standard drugs. In fact, the average approval time is exactly the same for priority NMEs and standard NMEs (14.0 months). The range of variation is very similar between products in the EU, which is not the case in the US. Furthermore, in the EU the lower and upper limits for all innovations are set by drugs classified as standard and priority, respectively, just the contrary to the situation in the US. The lower limit (5.5 months) is defined in the EU by a priority-review drug only in the case of NMEs. All told, even for NMEs, the upper limit of the range (25.4 months) is set by a priority-review drug. For both NMEs as well as for new biologics, the dispersion of outlying values is less in the EU than in the US, which plainly reveals that a policy that clearly favours priority drugs is not applied.

Finally, the gap between approval times in the EU and in the US is smaller for new biologics innovations (15.1 months and 14.7 months, respectively) than for the remaining pharmaceutical innovations. This is most likely due to the fact that there were already precedents under the concerted procedure (in force until 1994), which in turn, reflects the special attention paid to high-technology and biologically-derived medicines in the EU since 1987. Indeed, the centralised 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" [11].

5. Discussion

Although the goals set in the centralised procedure are being met in the EU, the results obtained in the last part of this study reveal that there is hardly any difference in approval times based on the products' degree of therapeutic relevance. This is worthy of special attention from a public health standpoint, since it is reasonable to assume that earlier or later availability of a standard drug is not of equal importance as in the case of a priority drug. In fact, in a study about the relationship between FDA approvals of NMEs and changes in the age distribution of deaths, Lichtenberg has demonstrated that approval (and the subsequent available stock) of priority-review drugs has a significant positive impact on longevity, whereas approval of standard-review drugs does not [12]. The new legislation that will govern the centralised procedures starting at the end of 2005 (Regulation No. 726/2004) foresees accelerated assessment procedures for medicinal products of major therapeutic interest and procedures for obtaining temporary authorisations subject to certain annually reviewable conditions. If the request of an accelerated assessment procedure is accepted, the timelimit of 210 days established for scientific assessment and opinion is reduced to 150 days [Article 14 (9)]. The foreseen decrease in the review time is applied to the scientific assessment stage and not to the decision-making process. It must be indicated that it is precisely the decision-making stage that is to be shortened in general in the new procedure foreseen in the regulation. This is a clear indication of just how bureaucratic the process is. Moreover, the anticipated accelerated assessment procedure is similar to the existing formula for the approval of drugs under "exceptional circumstances", particularly because neither case

foresees a prior classification of all new drug and new biologics applications, similar to the one in the US. It should be added that the approval of drugs under "exceptional circumstances" pathway has hardly ever been used [13].

In the US, the review-time goals established in PDUFA I, II, and III do not appear to have been met with regard to standard-review drugs. The fact that they have been met for priority-review drugs means that the established priority-review system functions satisfactorily. In fact, the US is most commonly the first country in the world for which approval of a new drug is requested. Between 1997 and 2001, 70% of the applications were presented in the US first and only 19%, in the EU [14]. Nevertheless, the strategies followed by pharmaceutical companies for launching their new products are guided by other considerations in addition to approval times. They also take into account market size and, should it be the case, price regulations and reimbursement regimes -aspects that appear to favour the rapid availability of new drugs in the US [15]. For example, since the middle of the 90s, "... the US market had the highest percent annual growth rates, coming to account for approximately 40% of the total world market for ethical pharmaceuticals in 1999. Europe's share declined to less than 27 percent …", from almost 30 percent in 1995.[14] Furthermore, one thing is drug approval and another thing is its availability on the market. Thus, Member States have sovereignty over pricing and reimbursement regimes, leading to different delay periods and subsequently, to unequal access to new drugs across the EU. In this regard, it has been estimated that "… there can be as much as 4 years between the first patient in the

[14] Data from the IMS International. Taken from [16].

first Member State having access to an innovative medicine, and the first patient in the last Member State enjoying the same access" [17].[15]

Finally, as regards product withdrawals from the market, it seems that the percentage of withdrawals is similar in the EU and in the US, despite the differences in the approval procedures. In this sense, mention must be made of the possible impact recent recalls and withdrawals of several major drugs from the world market might have on the future evolution of approval procedures and, hence, on approval times. Thus, the withdrawal of Cerivastatin (and the controversy subsequently unleashed),[16] along with "... a series of controversies involving the safety of hormone replacement therapy, antidepressants, antiarthritis drugs ... have raised serious questions about the independence of the US drug regulator and led to congressional investigations" [18]. In light of the announcement made by the FDA that different measures would be adopted to improve the post-marketing surveillance system, the Editorial of *The Journal of the American Medical Association (JAMA),* dated 1 December 2004 was highly critical of most of the measures, proposing that " ... the drug approval process [be] ... decoupled from the postmarketing safety and surveillance system" and that an independent agency for drug safety be established [19]. Also, the extension of mandatory postmarketing studies to all new products is recommended.[17] Remember that, unlike the US, renewal of marketing authorisations is compulsory after five years under the EU centralised procedure, enabling the EMEA to take new evidence into consideration. Nevertheless,

[15] G10 Medicines was created in 2001 under the auspices of the European Commission. Membership includes top decision-makers representing national governments, health insurers, industry and patients. It had an important influence on the new regulation of drugs in the EU.

[16] See, i.e., *JAMA*, vol. 292, no. 21, December 1, 2004.

[17] In this respect, it has been pointed out that " ... it appears that fewer than half of the postmarketing studies that manufacturers have made commitments to undertake as a condition of approval have been completed and many have not even been initiated" [19].

(EC) Regulation No. 726/2004 establishes that, "The marketing authorisation may be renewed after five years on the basis of a re-evaluation by the Agency of the risk-benefit balance" but, in principle, "Once renewed, the marketing authorisation shall be valid for an unlimited period…" [Article 14 (2 and 3)] compared to the five-year rennovation periods currently in force.

In this context, an unprecedented move took place in Europe with the creation of The Medicines in Europe Forum, a public interest group of medicines created in 2002 with the aim of influencing the EU process of drug regulation, from a patient perspective. Its membership includes consumer organisations, patient groups, organisations that pay for medicines and professional bodies.[18] In the European context, the demand for principles such as transparency and independence also reveals the need to regain confidence in the regulators. Consequently, it can be expected that in the coming years, drug safety and the very structure of the Agencies themselves will be subject to closer scrutiny than the time they use in the approval process.

[18] See http://www.epha.org/a/509.

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Table 1
Mean Approval Times (in Months) for Pharmaceutical Innovations (PIs) Authorised in the EU under the Centralised Procedure and in the US (1995-2003)

	European Union (Centralised Procedure)												United States									
	PIs (NMEs and New Biologics)				PIs-List A				PIs-List B				NMEs		Standard NMEs		Priority NMEs		New Biologics		PIs (NMEs and New Biologics)		
Year	**No**	**Appr. Time**	**Clock Stop**	**Review Time**	**No**	**Appr. Time**	**Clock Stop**	**Review Time**	**No**	**Appr. Time**	**Clock Stop**	**Review Time**	**No**	**Appr. Time**	**No**	**Appr. Time**	**No**	**Appr. Time**	**No**	**Appr. Time**	**No**	**Appr. Time**	**Year**
1995 (CM)	3	10.5 (18.5)	2.0	8.5	2	10.3 (20.4)	1.4	8.9	1	10.9 (14.7)	3.1	7.8	28	19.2	19	23.6	9	10.1	2	25.4	30	19.7	**1995**
1996 (CM)	19	13.0 (15.7)	2.9	10.1	7	15.9 (23.2)	5.2	10.8	12	11.4 (11.7)	1.7	9.7	53	17.8	36	19.7	17	13.7	9	24.5	62	18.7	**1996**
1997	16	14.7	4.3	10.4	10	15.9	5.5	10.4	6	13.1	2.8	10.3	39	16.2	30	18.2	9	9.4	10	32.4	49	19.5	**1997**
1998	17	12.6	3.0	9.6	2	13.0	3.7	9.3	15	12.6	3.0	9.6	30	11.7	14	14.3	16	9.5	9	13.5	39	12.2	**1998**
1999	23	14.8	5.4	9.4	11	15.2	6.0	9.2	12	14.5	4.9	9.6	35	12.6	16	16.9	19	9.0	5	17.1	40	13.2	**1999**
2000	22	16.0	5.7	10.2	9	13.8	4.5	9.3	13	17.9	6.8	11.0	27	17.6	18	22.7	9	7.4	6	25.8	33	19.1	**2000**
2001	30	15.2	5.4	9.8	12	15.1	5.3	9.8	18	15.3	5.5	9.8	24	16.4	17	19.7	7	8.3	8	19.6	32	17.2	**2001**
2002	22	15.7	5.7	10.0	7	17.6	7.7	9.9	15	14.8	4.8	10.0	17	17.8	10	20.3	7	14.2	9	30.1	26	22.1	**2002**
2003	17	15.3	5.1	10.2	3	17.8	7.2	10.6	14	14.6	4.5	10.1	21	16.9	12	20.5	9	12.0	14	34.7	35	24.0	**2003**
Period (APE)	169	14.7	4.8	9.9	63	15.3	5.5	9.8	106	14.4	4.4	10.0	274	16.2	172	19.6	102	10.4	72	26.0	346	18.2	**Period (APE)**
Period (APEE)	158	14.7	4.8	9.9	56	15.3	5.5	9.8	102	14.4	4.5	9.9											

(Table 1 – continuation)

CM = Corrected Means: all authorisations granted under the centralised procedure in 1995 come from dossiers that began in accordance with the former concertation procedure, from which they were transferred to the new centralised procedure. In these cases, the EMEA database records the application validation date as 1 January 1995, hence the times are underestimated. This is also the case in 8 of the 19 innovations authorised in 1996. Therefore, for these two years, the actual time used to process the dossiers was also calculated. The results of these calculations are shown in parentheses for these two years. Nevertheless, it is very likely that the figures calculated in this way are greater than they would have been in normal circumstances. That is, the very transition process from the former system to the new one implies that, in principle, the years 1995 and 1996 are not representative. Consequently, the last line reflects the average figure for the entire period, omitting the 11 PIs involved.

APE = Average Period Estimate; the calculation made on average for the entire time period.

APEE = The calculation made on average for the entire time period, excluding the 11 pharmaceutical innovations initiated under the former concertation procedure.

Sources: EU data: Author´s calculations based on the List of Authorised Products (EPARs; European Public Assessment Reports), available at the EMEA website: http://www.emea.eu.int/. US data: Total approval times for NMEs and for new biologics obtained from the Pharmaceutical Research and Manufacturers of America (PhRMA), available at http://www.phrma.org/; Total approval times for priority NMEs, Standard NMEs and PIs: Author´s calculations on the basis of data from the FDA (http://www.fda.gov/) and PhRMA.

Table 2
Median Approval and Review Times (in Months) for Pharmaceutical Innovations (PIs) Authorised in the EU Under the Centralised Procedure and in the US (1995-2003)

	European Union (Centralised Procedure)									United States												
	PIs (NMEs and New Biologics)			PIs-List A			PIs-List B			NMEs			Standard NMEs			Priority NMEs			New Biologics		PIs (NMEs and New Biologics)	
	No	Appr. Time	Review Time	No	Appr. Time	Review Time	No	Appr. Time	Review Time	No	Appr. Time	Review Time	No	Appr. Time	Review Time	No	Appr. Time	Review Time	No	Appr. Time	No	Appr. Time
1995 (CM)	3	10.9 (18.6)	8.6	2	10.3 (20.4)	8.9	1	10.9 (14.7)	7.8	28	15.9	15.2	19	17.8	15.9	9	6.0	6.0	2	25.4	30	16.6
1996 (CM)	19	12.9 (12.9)	10.3	7	15.9 (19.1)	10.7	12	12.1 (12.1)	9.5	53	14.3	12.0	35	15.1	14.6	18	9.6	7.7	9	18.1	62	14.6
1997	16	14.9	10.3	10	15.8	10.3	6	13.0	10.0	39	13.4	12.8	30	15.0	14.4	9	6.7	6.4	10	13.3	49	13.4
1998	17	13.2	10.0	2	13.0	9.3	15	13.2	10.0	30	12.0	11.9	14	13.4	12.3	16	6.2	6.2	9	7.8	39	12.0
1999	23	14.3	9.6	11	15.6	9.6	12	13.4	9.6	35	11.6	10.0	16	16.3	14.0	19	6.9	6.3	5	13.9	40	12.0
2000	22	17.2	10.0	9	14.7	9.7	13	18.5	10.3	27	15.6	13.9	18	19.9	15.4	9	6.0	6.0	6	24.3	33	15.6
2001	30	15.7	9.9	12	15.7	10.0	18	15.6	9.8	24	14.4	-	17	19.0	15.7	7	6.0	6.0	8	21.4	32	16.8
2002	22	15.9	10.2	7	18.1	9.9	15	15.7	10.2	17	16.3	-	10	15.9	12.5	7	16.3	13.8	9	28.8	26	17.3
2003	17	15.3	9.8	3	16.5	10.2	14	14.2	9.8	21	9.9	-	12	23.1	13.8	9	6.7	6.7	14	21.3	35	17.8

CM = Corrected Medians: all authorisations granted under the centralised procedure in 1995 come from dossiers that began in accordance with the former concertation procedure, from which they were transferred to the new centralised procedure. In these cases, the EMEA database records the application validation date as 1 January 1995, hence the times are underestimated. This is also the case in 8 of the 19 innovations authorised in 1996. Therefore, for these two years, the actual time used to process the dossiers was also calculated. The results of these calculations are shown in parentheses for these two years. Nevertheless, it is very likely that the figures calculated in this way are greater than they would have been in normal circumstances. That is, the very transition process from the former system to the new one implies that, in principle, the years 1995 and 1996 are not representative.

Sources: EU data: Author´s calculations based on the List of Authorised Products (EPARs; European Public Assessment Reports), available at the EMEA website: http://www.emea.eu.int/. US data: Information obtained from various FDA publications available at http://www.fda.gov/, except for the total approval times for NMEs authorised in 2001, 2002 and 2003 and approval times for new biologics and PIs as a whole, which have been calculated by the author based on the data available at http://www.phrma.org/

Table 3
Safety-Based NME Withdrawals in the UE (Centralised Procedure) and in the US (Authorised during the period 1995-2003)

Year of Authorisation	UE-PIs withdrawals for explicit safety reasons	Year of Withdrawal (date of reincorporation, if applicable)	USA-NMEs withdrawals for explicit safety reasons	Year of Withdrawal (date of reincorporation, if applicable)
1995	0	-	0	-
1996	0	-	0	-
1997	Levacetylmethadol[a] Tolcapone[b]	2001 1998 (2004)	Bromfenac[c] Mibefradil[c] Grepafloxin[c] Troglitazone[c] Cerivastatin[c]	1998 1998 1999 2000 2001
1998	Trovafloxacin[d] Alatrofloxacin[d]	2001 2001	0	-
1999	0	-	Rapacuronium[c]	2001
2000	0	-	Alosetron[c,e]	2000 (2002)
2001	0	-	0	-
2002	0	-	0	-
2003	0	-	0	-

[a] Recommendation was made not to market in 2001 and, in fact, it was no longer sold on the EU market. This NME had been marketed in Denmark, Germany, Portugal Spain, The Netherlands and the United Kingdom, and has been available on the US market since 1994. The total approval time by the FDA was 18 days and 912 days by the EMEA [9].
[b] It was pulled from the market in 1998 (on the recommendation of the Committee for Proprietary Medicinal Products). It was reintroduced in 2004, with special restrictions. It was authorised in the US on 29 January 1998. On 17 November of that same year, information regarding liver damage was added and hence, required patient consent.
[c] None of these active ingredients were authorised in the EU under the centralised procedure, although some of them were marketed. For example, Cerivastatin was also removed from the European markets in 2001.
[d] Marketed in the US, albeit with special safety restrictions. Following the recommendation that its authorisation be pulled in 1999, the European Commission decided to withdraw authorisation in 2001. These NMEs had been marketed in Austria, Denmark, Finland, Germany, Portugal, Spain, Sweden, and The Netherlands.
[e] In 2000, it was taken off the market and its sale was authorised again in 2002, with special safety restrictions.

Sources: Elaborated by the author based on the information available at: http://www.emea.eu.int/htms/human/withdraw/withdraw.htm and http://www.emea.eu.int/htms/human/drugalert/drugalert.htm (for the EU), and http://www.fda.gov/cder/reports/ and http://www.fda.gov/medwatch/ (for the US).

Table 4
Mean Approval Times (in Months) for Pharmaceutical Innovations (PIs) Authorised by Both the EMEA (Centralised Procedure) and the FDA during the period 1995-2003 (range in parentheses)

NMEs				New Biologics				PIs (NMEs and New Biologics)			
Number		**US Mean time**	**EU Mean Time**	**Number**		**US Mean time**	**EU Mean Time**	**Number**		**US Mean time**	**EU Mean Time**
Total[a]	84	11.6 (1.4 – 36.5)	14.0 (5.5 – 25.4)	**Total[b]**	33	14.7 (4.7 – 34.1)	15.1 (4.7 – 21.4)	**Total[c]**	117	12.5 (1.4 – 36.5)	14.3 (4.7 – 25.4)
- Priority[a]	49	8.1 (1.4 – 28.8)	14.0 (5.5 – 25.4)	**- Priority**	11	10.7 (4.7 – 34.1)	14.9 (11.5 – 18.7)	**- Priority[c]**	60	8.6 (1.4 – 34.1)	14.1 (5.5 – 25.4)
- Standard[a]	35	16.7 (7.1 – 36.5)	14.0 (6.8 – 20.3)	**- Standard[b]**	12	21.2 (9.9 – 30.9)	14.7 (4.7 – 19.7)	**- Standard[c]**	47	17.7 (7.1 – 36.5)	14.2 (4.7 – 20.3)
- Not classified	0	-	-	**- Not classified[b]**	10	12.3 (5.4 – 18.1)	15.9 (11.1 – 21.4)	**- Not classified[c]**	10	12.3 (5.4 – 18.1)	15.9 (11.1 – 21.4)

[a] 4 NMEs transferred from the former EU concertation procedure that might distort comparisons have been excluded; 2 classified as priority and 2, as standard.
[b] 3 NMEs transferred from the former EU concertation procedure that might distort comparisons have been excluded; 2 classified as standard and 1 that was not classified.
[c] 7 NMEs transferred from the former EU concertation procedure that might distort comparisons have been excluded; 2 classified as priority; 4, as standard, and 1 that was not classified.

Sources: Author´s calculations based on data obtained from the EMEA website (http://www.emea.eu.int/), the FDA website (http://www.fda.gov/) and the PhRMA website (http://www.phrma.org/).