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Research paper

Biopharmaceuticals approved in the EU 1995–1999: a European Union–United States comparison

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Abstract

The European Union's (EU) centralized procedure for new drug review was implemented in 1995 to unify the regulatory process and provide EU-wide marketing authorizations for innovative medicinal products. Goals were instituted to ensure the timeliness of the various steps of the process. The EU approved 27 biopharmaceutical products through the centralized procedure during 1995–1999. This study documents the success of the EU in meeting the timeline goals for the group and for separate categories of biopharmaceuticals (recombinant proteins, monoclonal antibodies, and antisense oligonucleotides). A subset of the 27 biopharmaceuticals approved in the EU were also approved in the United States (US). We compared EU and US approval times for these products by product category and by review status (exceptional/non-exceptional circumstance in the EU and priority/standard in the US). © 2001 Elsevier Science B.V. All rights reserved.

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1. Introduction

The procedures for the approval of biopharmaceutical medicines for marketing in the European Union (EU) have changed significantly during the last 15 years [1,2]. Prior to 1987 products were reviewed and approved on a country-by-country basis, a time consuming and expensive way to gain approval for marketing a product in multiple countries. A 'concertation procedure' was established in 1987 [3], under which product applications for biopharmaceuticals were reviewed by the Committee for Proprietary Medicinal Products (CPMP) but still approved on a country-by-country basis. In order to streamline the process further, the EU established the European Medicines Evaluation Agency (EMEA). As of January 1, 1995 the EMEA has used a centralized procedure [1] to evaluate biopharmaceuticals. Under the centralized procedure biopharmaceutical product applications undergo a timely review by the CPMP, which serves within the EMEA as the primary scientific review committee, and are granted a single marketing authorization for all 15 EU member countries.

The EMEA classifies medicinal products as either List A or List B [1]. List A products are those developed using recombinant DNA technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells, and hybridoma and monoclonal antibody methods. List B products include medicinal products that are new to the EU and those which, in the opinion of the agency, constitute a significant innovation or are of significant therapeutic interest. Use of the centralized procedure is mandatory for List A products but optional for List B products. All biopharmaceutical products approved in the EU since 1995 have gone through the centralized procedure to gain marketing authorization. Each step of the process in the centralized procedure is clearly defined and has a timeline goal associated with it (Fig. 1). Notification of the intention to submit a product dossier should be filed with the EMEA approximately 6 months prior to the actual submission. Upon receipt, the EMEA has 15 days to validate the dossier and start the review process. The date of validation marks day 1 of the process. The scientific review is done by the CPMP and should take no longer than 120 days. The clock is stopped after the initial review to allow the sponsoring company to answer questions or address any issues raised by the CPMP. This 'clockstop' time should not exceed 182 days. The clock is restarted after a response is received. The CPMP should formulate a final opinion within 90 days of the restart of the clock. After a positive opinion is given the EMEA has 30 days to finalize an assessment report and send it to the

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European Commission. Thus the total length of time the EMEA has to review a product application is 240 days. The CPMP may recommend that the marketing authorization be granted 'under exceptional circumstances', a designation which allows medicines to be approved when comprehensive data on quality, efficacy, and safety under normal conditions cannot be provided. The final marketing authorization is granted by the European Commission (EC). The decision should be made public by the EC 60–80 days after receipt of the assessment report from the CPMP. The marketing authorization is valid the same day the registration is signed by the Commissioner Directorate General and must be renewed every 5 years.

The procedures for the approval of biopharmaceuticals, as well as conventional drugs, have also changed in the United States, though not as dramatically as in the EU. The Prescription Drug User Fee Act of 1992 (PDUFA) [4] and the renewal legislation, the Food and Drug Administration Modernization Act of 1997 (FDAMA) [5] established a number of accelerated review initiatives, as well as performance goals associated with the review initiatives. One of the initiatives was priority review, which applies to products that would be a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease. The majority of the biopharmaceuticals approved in the US during the last 5 years have had a priority review and, as a result, there has been a substantial reduction in Food and Drug Administration (FDA) approval times for biopharmaceutical products [6,7].

In the US, biopharmaceuticals are reviewed at either of two FDA centers, the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER). Upon receipt of an original product application (Day 1), the appropriate FDA center performs the review and issues a first action letter. The clock is stopped on the date of the first action letter. The first action letter may indicate that the product has been approved or it may detail deficiencies in the product application. If the application is not approved by the first action, then the sponsoring company must address the deficiencies and resubmit the application. The time that is required for the sponsoring company to prepare an application for resubmission is 'sponsor response' time (equivalent to 'clockstop' time). The clock starts again upon FDA's receipt of the resubmitted application and continues to run until a second action letter is issued. As was the case with the first action, if the application is not approved then the sponsoring company must resubmit the application. Theoretically, there is no limit to the number of times an application can be resubmitted. Performance goals for both centers were set in PDUFA and FDAMA [4,5]. The goals specify the maximum time allowed for review of all applications submitted in a fiscal year; goals vary by the review status of the product application, by the fiscal year of submission, and by the type of application (original or resubmission).

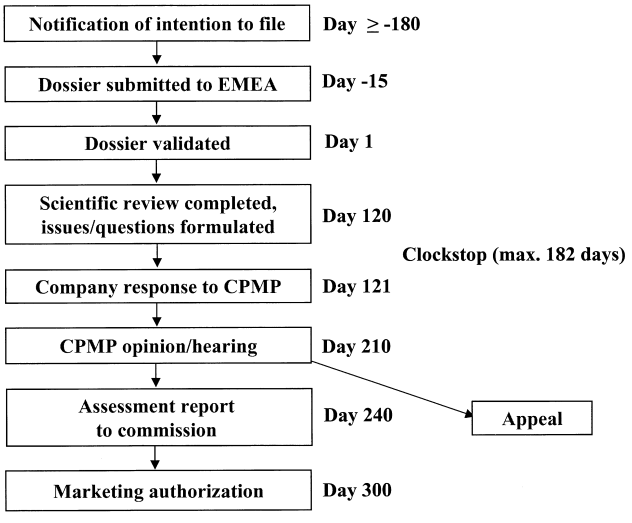

Fig. 1. Centralized procedure timeline.

The objectives of this study were: (1) to determine the mean approval times for 27 biopharmaceutical products approved using the centralized procedure in the EU during 1995–1999; (2) to assess the effect of product category (recombinant protein, monoclonal antibody, or antisense oligonucleotide) and review status (exceptional or non-exceptional) on mean approval times for the 27 products; and (3) to compare by product category and by review status (exceptional/non-exceptional vs. priority/standard) the mean approval times for 16 biopharmaceutical products approved in the EU during 1995–1999 with the mean US approval times for the same products.

2. Methods

The data presented in this study were derived from the EMEA database and the US biopharmaceuticals database, both of which are maintained by Tufts Center for the Study of Drug Development (Tufts CSDD). Data on therapeutic biopharmaceutical products approved in the EU were compiled in the Tufts CSDD EMEA database from documents available on the EMEA website (www.eudra.org). Specifically, EMEA annual reports, European public assessment reports (EPARs) and CPMP press releases were used as sources of information. This study includes 27 products in the following product categories: recombinant proteins (List A) including Humalog (List B), monoclonal antibodies (List A), and antisense oligonucleotides (List B). Non-therapeutic biopharmaceuticals such as vaccines and diagnostic monoclonal antibodies were not included. EMEA rating as exceptional, i.e. recommended for approval under exceptional circumstances, was available in EPARs; those products not listed as exceptional were rated in this study as non-exceptional for classification purposes. All products were reviewed under the centralized procedure.

Data on biopharmaceutical products approved in the US were available from the Tufts CSDD US biopharmaceuticals

database. This database includes information pertaining to the development and regulatory review of products currently in development, terminated products, and FDA-approved products. This information is collected from surveys of biopharmaceutical companies and from publicly accessible sources and documents [8–11]. The database currently includes records for over 900 products from more than 350 companies. Nineteen of the biopharmaceutical products approved in the EU during 1995–1999 had already been approved in the US or were approved in the US during the same period. Two of the biopharmaceuticals were approved under two separate applications in the EU but only one in the US. Humalog and Liprolog (both are insulin lispro) differ only in the EU marketing authorization holder and tradename; Ecokinase and Rapilysin (both are reteplase) have the same manufacturer. Liprolog and Rapilysin were not included in the analyses. Betaferon was also not included in the analyses because US clockstop time was not available. Thus data for 16 products were used for the EU–US comparisons. These products were approved in the EU during 1995–1999 and in the US during 1994–1999. The review status of each application was available from the FDA.

The following time intervals were calculated for the analyses of the EU-approved products: (1) mean active review time (length of time application was under active review by the CPMP; does not include application validation time, clockstop time, or time required by CPMP to prepare assessment report); (2) clockstop time (length of time the sponsoring company took to answer questions or address issues raised during the CPMP review); (3) EC review time (length of time EC took to issue marketing authorization based on product dossier and CPMP opinion); and (4) total approval time (length of time from application validation to approval; includes clockstop time and time required by CPMP to prepare assessment report).

The following time intervals were calculated for the comparison of products reviewed and approved in both the EU and the US: (1) EU approval time (length of time between application submission date and approval date minus clockstop time); and (2) US approval time (length

Table 1
Biopharmaceutical products approved in the EU and the US

EU (US) Trade name	Generic name	Sponsoring company	EU approval date	US approval date	EMEA rating	FDA rating
Antisense oligonucleotide						
Vitravene (Vitravene)	Fomivirsen	Ciba Vision Europe	07/29/99	08/26/98	Exceptional	Priority
Monoclonal antibody						
Simulect (Simulect)	Basiliximab	Novartis Europharm Ltd.	10/09/98	05/12/98	Non-exceptional	Priority
Zenapax (Zenapax)	Daclizumab	Roche Registration Ltd.	02/26/99	12/10/97	Non-exceptional	Priority
Synagis (Synagis)	Palivizumab	Abbott	08/13/99	06/19/98	Non-exceptional	Priority
Remicade (Remicade)	Infliximab	Centocor BV	08/13/99	08/24/98	Exceptional	Priority
Recombinant protein						
Gonal-F (Gonal-F)	Follitropin alpha	Serono Laboratories Ltd.	10/23/95	09/29/97	Non-exceptional	Standard
Betaferon (Betaseron)[a]	Interferon beta-1b	Schering AG	11/30/95	07/23/93	Exceptional	Priority
Novoseven (Novoseven)	Eptacog alfa	NovoNordisk (Denmark)	02/23/96	03/25/99	Non-exceptional	Priority
Humalog (Humalog)	Insulin lispro	Eli Lilly (Netherlands)	04/30/96	06/14/96	Non-exceptional	Standard
Puregon (Follistim)	Follitropin beta	Organon Ltd. (Netherlands)	05/03/96	09/29/97	Non-exceptional	Standard
Ecokinase (Retavase)	Reteplase	Galenus Mannheim	08/29/96	10/30/96	Non-exceptional	Standard
Rapilysin (Retavase)[a]	Reteplase	Boehringer Mannheim	08/29/96	10/30/96	Non-exceptional	Standard
Insuman	Insulin, human	Hoechst AG	02/21/97	NA[c]	Non-exceptional	NA
Refludan (Refludan)	Lepirudin	Behringwerke AG	03/13/97	03/06/98	Non-exceptional	Priority
Avonex (Avonex)	Interferon beta-1a	Biogen, France SA	03/13/97	05/17/96	Exceptional	Priority
Liprolog (Humalog)[a]	Insulin lispro	Eli Lilly&Company, Ltd.	05/07/97	06/14/96	Non-exceptional	Standard
Revasc	Desirudin	Ciba Novartis Europharm	07/09/97	NA	Non-exceptional	NA
Neorecormon	Epoetin beta	Boehringer Mannheim GMBH	07/16/97	NA	Non-exceptional	NA
Benefix (Benefix)	Nonocog alfa	Genetics Institute	08/27/97	02/11/97	Exceptional	Priority
Cerezyme (Cerezyme)	Imiglucerase	Genzyme BV	11/17/97	05/23/94	Non-exceptional	Priority
Rebif	Interferon beta-1a	Ares-Serono (Euro) Ltd.	05/04/98	NA	Exceptional	NA
Forcaltonin	Calcitonin (salmon)	Unigene UK Ltd.	01/11/99	NA	Non-exceptional	NA
Infergen (Infergen)	Interferon alfacon-1	Yamanouchi Europe BV	02/01/99	10/06/97	Non-exceptional	Standard
Regranex (Regranex)	Becaplermin	Janssen-Cilag	03/29/99	12/16/97	Non-exceptional	Standard
Beromun	Tasonermin	Boehringer Ingelheim GMBH	04/13/99	NA	Non-exceptional	NA
Refacto (Refacto)[b]	Moroctocog alfa	Genetics Institute of Europe	04/13/99	03/06/00	Non-exceptional	Standard
Novorapid	Insulin aspart	Novo Nordisk A/S	09/07/99	NA	Non-exceptional	NA

[a] Not included in analyses of EU or USA approval times (see Section 2).
[b] Not included in analyses of US approval times (approved in US after 1999, see Section 2).
[c] NA, Not approved.

of time between new drug or biologics application submission date and approval date minus clockstop time).

3. Results

The European Union approved 27 biopharmaceutical products during 1995–1999 (Table 1). The majority of the products (81%) were recombinant proteins. Four therapeutic monoclonal antibodies and one antisense oligonucleotide were also approved. The CPMP recommended approval under exceptional circumstance for six of the products. Of these 27 biopharmaceuticals, 19 (including duplicates) were also approved in the US. The FDA gave 11 of these products a priority review.

3.1. Comparison of biopharmaceutical product categories approved in the EU during 1995–1999

We calculated the mean active review, clockstop, EC review, and total approval times for the categories of biopharmaceuticals (recombinant proteins, monoclonal antibodies, and the antisense oligonucleotide) and for the total number of products (Fig. 2). The mean active review time was consistent among the product categories. Mean clockstop time and EC review times of the product categories varied somewhat more but not greatly. The mean total approval time was also consistent; variation between longest and shortest total approval time was only 28 days.

Recombinant proteins required the longest active and EC reviews but had the shortest clockstop times. The net result was that recombinant proteins had the longest total approval time. Monoclonal antibodies had the longest mean clockstop time (165 days), the shortest mean EC review time (59 days), and a mean total approval time of 432 days. Compared to the mean times for all products, the antisense oligonucleotide required less active and EC review time but more clockstop time. The net result was that the antisense oligonucleotide had the shortest mean total approval time (426 days). For all biopharmaceutical products, the time from EMEA validation of the application to marketing authorization was an average of 450 days.

3.2. Comparison of products approved in the EU and US

Of the 27 biopharmaceuticals approved in the EU during 1995–1999, 19 were also approved in the US prior to the end of 1999. The mean EU and US approval times for 16 of the 19 products (see Section 2 for selection criteria) were calculated for the total number of products and for the products when categorized as either recombinant proteins, monoclonal antibodies, or antisense oligonucleotides (Fig. 3). Approval times were defined as agency review times only and thus do not include clockstop/sponsor response time. The mean EU approval time for all products (322 days) was 48 days shorter than the mean US approval time (370 days). As a group, the recombinant proteins required a longer mean US approval time when compared to the mean EU approval time. In contrast, the monoclonal antibodies and the antisense oligonucleotide were approved notably faster in the US compared to the EU (35 and 53%, respectively). The difference in the approval times might be attributable to the US review status of the products. The monoclonal antibodies and the antisense oligonucleotide were all priority-reviewed products whereas only five of the 11 recombinant proteins were priority-reviewed.

We classified the 16 products first by the exceptional circumstance/non-exceptional circumstance designation used in the EU, then by the priority/standard review designation used in the US (Fig. 4). The EMEA recommended approval under exceptional circumstance for four of the 16

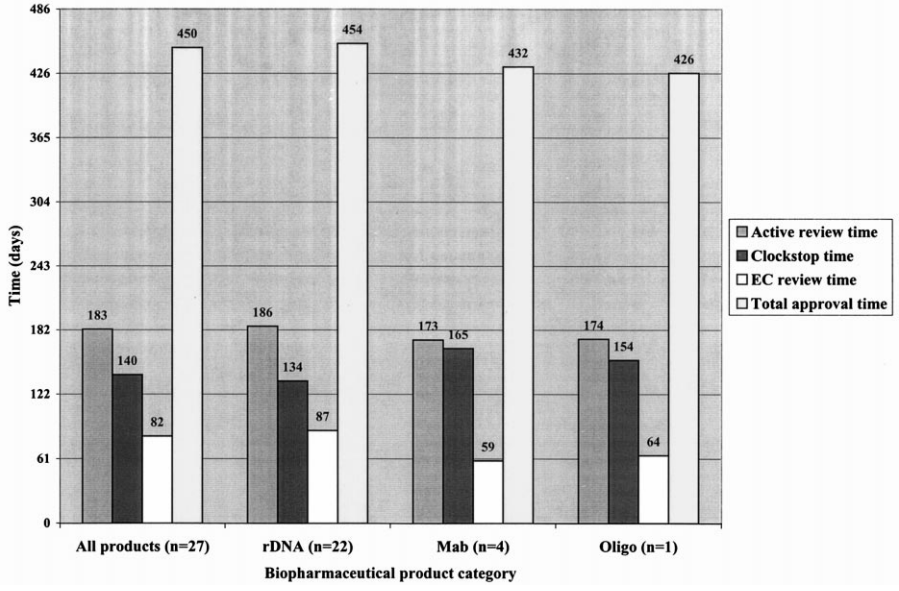

Fig. 2. Mean times for various stages of the centralized procedure for biopharmaceuticals approved in the EU during 1995–1999.

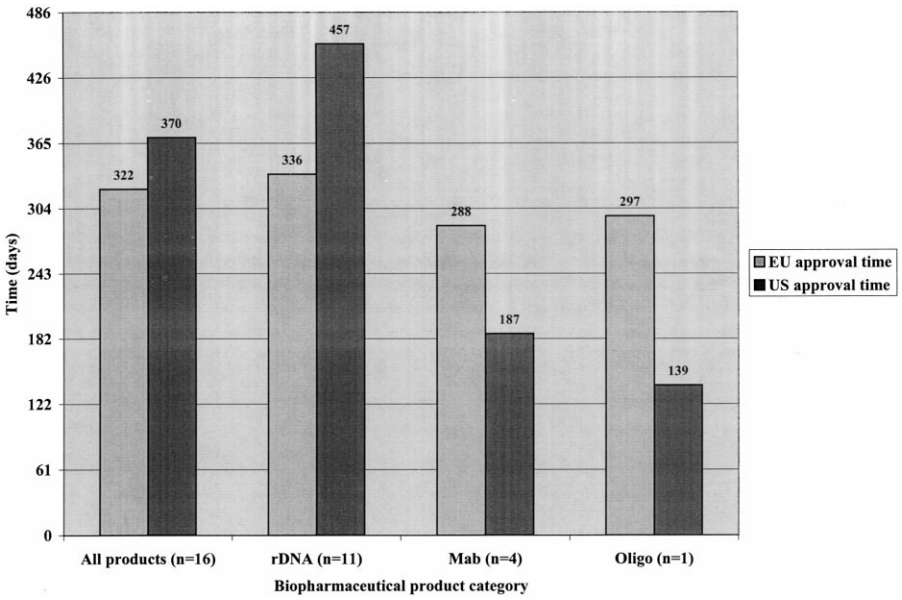

Fig. 3. Comparison of categories of biopharmaceutical products approved in the EU and US.

products. These products were approved slightly faster on average than non-exceptional products (9 days). The 'exceptional circumstance' products were all priority-reviewed in the US. The US approval time for the same four products was 32% faster than the EU approval time. In contrast the US approval time for the non-exceptional circumstance products was 30% longer than the EU approval time. The FDA gave priority review status to 10 of the 16 products. The mean US approval time for all 10 priority reviewed products was only 6% faster than the EU approval time. The US took longer (48%) than the EU, on average, to approve the standard-review products.

4. Discussion

The processes by which medicinal products undergo scientific review and receive marketing approval in the EU and US have changed substantially in recent years. The EU has implemented a centralized procedure with

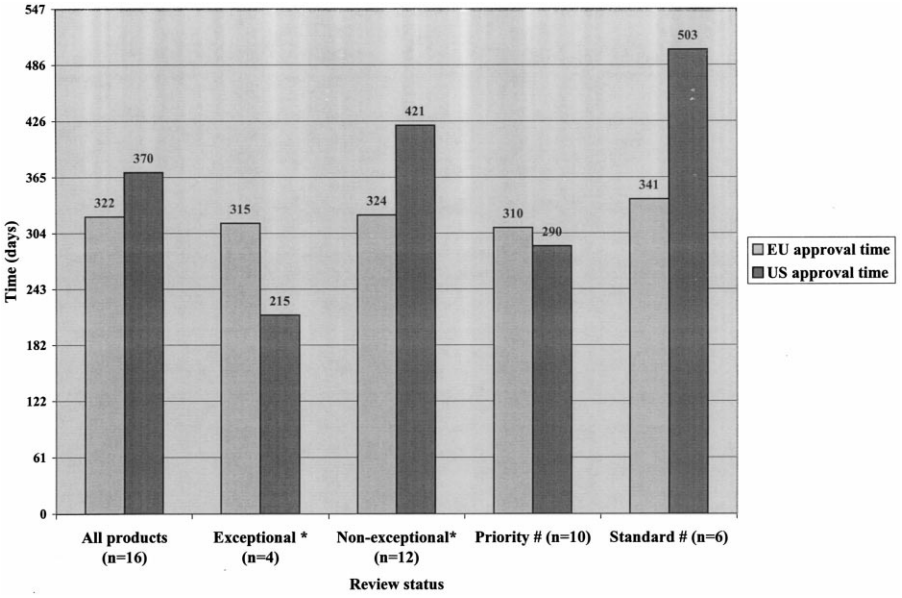

Fig. 4. Comparison of the effects of review status of biopharmaceutical products approved in the EU and US. *Exceptional and non-exceptional are exclusively EU review status designations. #Priority and standard are exclusively US review status designations.

specific review timeline goals; the US has defined a number of accelerated review initiatives for medicines and set performance goals for the review of product applications. The changes were made to speed up the approval process and provide the public in both the EU and US with timely access to innovative medicines. This study reported the overall success of the EU in meeting timeline goals and compared approval times for biopharmaceutical products approved in both the EU and US during this period of changes in the regulatory systems.

Effective use of the centralized procedure requires the combined efforts of the EMEA, sponsoring company, and EC. Our results indicate that the EMEA reviewed biopharmaceuticals promptly: 13% faster than the goal of 210 days. The sponsoring companies responded reasonably quickly to requests for additional information (23% faster than suggested limit of 182 days). The EC review time was slightly longer (82 days) than the limit of 60–80 days but that limit is more of a guideline than a rule. The Commission Directorate must sign the marketing authorization, so the timeline for this part of the process depends on his or her availability. Our results indicate that the overall timeline goals have been met and that use of the centralized procedure for approval of biopharmaceuticals takes a consistent and predictable length of time.

We compared EU and US approval times for biopharmaceuticals approved through both systems. The comparison between the mean elapsed time from the date of submission to either the EMEA or FDA and the date of approval for marketing in either the EU or US, minus clockstop times since neither agency had control over that part of the process. The mean approval time for all products was 13% faster in the EU compared to the US (10.6 vs. 12.2 months). Considering that the EU does not clearly define classes of products for faster review as the US does, this result indicates that the centralized procedure is working efficiently and, overall, biopharmaceuticals are being approved in the EU in a timely manner. As was observed with the times for individual parts of the centralized procedure, the mean EU approval time was very consistent for the different categories of biopharmaceuticals. In contrast the mean US approval times for the biopharmaceutical categories were inconsistent, an effect that was probably due to the review status of the products [6,7].

As of the end of 1999 there were a limited number of ways to classify medicines within the centralized procedure. Approval under exceptional circumstance, which allows medicines to be approved when comprehensive data on quality, efficacy, and safety under normal conditions cannot be provided, was given to six of the 27 biopharmaceuticals approved in the EU during 1995–1999. The 'exceptional circumstance' clause was not intended to speed up the review process and our data suggest that the designation does not correlate with a notable effect on the mean approval time. A CPMP Guideline [12] for accelerated evaluation of products indicated for serious diseases (life-threatening or heavy disabling diseases) exists but no biopharmaceuticals have been approved using this guideline. Recent US legislation [4,5] specifically mandated that the FDA speed up the approval process by establishing a number of accelerated review initiatives including priority-review and by instituting performance goals. Overall, mean approval times in the US have indeed decreased since those acts were passed, but, probably due to the difference in the performance goals for priority vs. standard review of applications, US approval times vary in review status [7]. The differences in the review status available in the EU and US might have contributed to the variation observed in the mean approval times for the same products approved in both locations.

The EU is currently working on expanding the available options for classifying medicines for the review and approval process. An orphan drug regulation was accepted by the European parliament on December 15, 1999. The regulation encourages development of medicines for diseases afflicting small numbers of patients (prevalence in general population of five per 10 000) by providing economic incentives to sponsoring companies. In addition, the EMEA has recently shown a willingness to use standards similar to those used by the FDA for accelerated approval [13]. The challenge for the EMEA and the EC will be to maintain current approval time for products that are not in special classifications while accelerating approval for special classes of medicines such as those intended for the treatment of rare, serious or life-threatening diseases.

Acknowledgements

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