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Research paper

Differences in product information of biopharmaceuticals in the EU and the USA: implications for product development

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Abstract

The Summary of Product Characteristics (SPC) approved by the European Medicines Agency (EMEA) and the Package Insert (PI) approved by the Food and Drug Administration (FDA) were examined for 32 biopharmaceutical products. The aim was to identify differences in the product information since such information may have an impact on the planning of global clinical development programmes. The EU SPC contained more detailed instructions to the prescriber, including the positioning of the product with regard to the stage of the disease and to other therapies. The approach to safety information, notably to contraindications and warnings was more conservative in the EU SPC. The conservative approach in the EU may reflect the central position of the SPC in risk management of new pharmaceuticals. A typical feature of the US PI was the detailed description of the efficacy and safety result of the pivotal clinical trials.

Keywords: Biopharmaceuticals; Regulation; EMEA; FDA; Marketing authorisation; Product information; Labelling

1. Introduction

Development programmes of medicinal products increasingly target the global market whereas regulation of medicinal products continues to operate on a local basis. Efforts for harmonisation of requirements for marketing authorisation have been made through bilateral and multilateral collaboration, notably via International Conference on Harmonisation of Marketing Authorisation Requirements (ICH) and mutual recognition agreements. In spite of considerable success, the complete harmonisation is still far away.

Within the European Union (EU), the centralisation of the evaluation of medicinal products derived from biotechnology has progressed more rapidly than the regulation of small chemical entities. The concertation procedure was established in 1987 when the first products manufactured by recombinant DNA methods reached the stage of marketing authorisation. The mandatory centralised marketing authorisation procedure for biotechnology products was established in 1993. As of the beginning of 1995, the European Medicinal Products Agency (EMEA) has been the regulatory authority for medicinal products derived from biotechnology, more specifically products manufactured by recombinant DNA technology, by controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes, including transformed mammalian cells, and by hybridoma and monoclonal antibody methods [1]. The EU centralised procedure utilises a single application, a single evaluation and a single authorisation allowing direct access to the single market of the Community.

In the USA, FDA has different statutory approval mechanisms and different governing statutes for drugs and biological products. Conventional drugs and some biologicals, such as insulins and hormones, are regulated on the basis of the Federal Food, Drug, and Cosmetic Act. Biologicals are regulated on the basis of the Public Health Service Act [2]. Within the FDA, the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA) has, up to 2003, been responsible for

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most biologicals, including monoclonal antibodies for in vivo use, cytokines, growth factors and enzymes. However, the main responsibility of biotechnology-derived products has since been transferred to the Center for Drug Evaluation and Research (CDER) [3].

Previous studies have revealed differences in approval and review times of pharmaceuticals [4,5], critical aspects in the review of marketing authorisation applications submitted to the EMEA [6], a EU–USA comparison of approval times and review status of biopharmaceuticals [7], trends in development and approval times for new therapeutics in the USA [8,9], development and approval times for biopharmaceuticals [10], EMEA evaluation times for biopharmaceuticals [11]. However, to our knowledge, the product information of biopharmaceuticals under the jurisdiction of the EMEA and the FDA have not been compared.

The product information in Summary of Product Characteristics (SPC) and Package Insert (PI) have major commercial implications for product developers, e.g. in the number of potential users, marketing and liability. Other stakeholders affected by the quality of the SPC and the PI are, first and foremost, patients and physicians as well as health authorities. For prescribers and users of medicinal products, the product information approved by the regulatory authorities provides a balanced and objective view on the safe and efficacious use of a given product. The approved product information is the basis for product safety surveillance and for the control of promotional activities. Consequently, the aim of the present study was to identify possible differences in product information of biopharmaceuticals in the EU and the USA. The EU SPC and the USA PI contain the essential information on the pharmaceutical and clinical aspects of medicinal products. The European Commission guideline on the SPC of December 1999 states that the SPC must provide information for health professionals on how to use medicinal products safely and effectively [12]. In the USA, the Code of Federal Regulations (CFR) title 21 [13] contains specific instructions on labelling, including the content of the PI for physicians. The present study is based on SPCs of biopharmaceuticals approved via the centralised procedure of the EU and PIs in the FDA.[1]

The present study examined the EU SPCs and PIs of the US of 32 biopharmaceuticals. A semi-quantitative grading was used to judge whether the information in the corresponding SPCs and PIs was similar or different. Overall, the differences between the EU SPC and the USA PI were not striking. However, our results suggest that the approach to safety information, notably to contraindications and warnings, was clearly stricter in the EU SPC.

[1] Note that the regulatory comments are personal opinions of the authors. These comments do not necessarily reflect the position of any regulatory body.

2. Methods

The SPCs of biopharmaceuticals licensed in the EU between 1995 and March 2004 were compared to the US PIs of the same products. A more detailed description of the regulatory review of medicinal products is given in the European Public Assessment Report (EPAR) and in the corresponding FDA review reports. These documents were examined for administrative information. In addition, the date and type of the regulatory approval as well as post-authorisation commitments/obligations were recorded. The biopharmaceuticals included in the present study are 'Part A' products of the EMEA (Council Directive 2309/93). The SPCs and PIs contain several sections (Table 1). EMEA and FDA categorise the content of the SPC and PI, respectively, very differently but the same topics can generally be found in both documents. No deliberate exclusion of any product was carried out. However, our sample represents a cross-sectional sample based on the web sites of the two regulatory agencies. In spite of the possibility that additional products approved both by the FDA and the EMEA exist, the current sample is representative for products licensed by the agencies. It should be noted that there are several biological products, notably vaccines and blood products that have been licensed by the FDA in the USA and by national regulatory agencies in the EU. These products are beyond the scope of this manuscript.

Table 1
Sections of the SPC and PI

SPC of the EMEA	PI of the FDA
1. **Name of medicinal product**	1. **Description**
2. Qualitative and quantitative composition	2. **Clinical pharmacology**
3. Pharmaceutical form	3. **Indications and usage**
4. **Clinical particulars, including therapeutic indications posology and method of administration, contraindications, warnings and precautions, undesirable effects, pregnancy and lactation**	4. **Contraindications**
5. **Pharmacological properties, including pharmacodynamic properties and clinical data**	5. **Warnings**
6. Pharmaceutical particulars	6. **Precautions, including pregnancy and lactation paediatric use**
7. **Other information on marketing authorisation holder and number and dates of the authorisation/renewal of the authorisation and revision of the text**	7. **Adverse reactions**
	8. Drug abuse and dependence
	9. Overdose
	10. **Dosage and administration**
	11. How supplied
	12. **Clinical studies**

Issues examined in this study have been marked with bold text.

The analysis was carried out by designing a standard form, which was used to list and describe selected topics of each section of the product labelling. Such topics included information on clinical trials, type of the marketing authorizations, therapeutic indications, posology, retrictions to prescribing, contraindications, warnings and precautions, drug interactions, adverse reactions, pharmacodynamics/clinical trials, preclinical information, medication during pregnancy and lactation and pediatric use. The form included a semi-quantitative grading of the key characteristics in order to judge whether the information in the corresponding SPCs and PIs was similar or different. These key characteristics of each topic refer to the possible differences, which may be significant for the marketing as well as clinical use of the products. For the majority of topics, these key characteristics were graded as 'same, less or more'. A more specific numerical grading of all topics was not considered to be valid, as the format of the SPCs and PIs is different. Thus, for this grading, indications, restrictions, contraindications and warnings and precautions were counted and the total number of each was compared between SPC and PI. On the other hand, specific numerical data for contraindications and warnings and precautions was evaluated by using the Wilcoxon test. With some key characteristics, classification into specific categories was also possible, e.g. for medication during pregnancy and lactation. The classification used for medication during pregnancy and lactation was (1) contraindicated, (2) not recommended, (3) allowed only exceptionally, (4) allowed with caution and (5) not applicable. Additional qualitative description was applied for *therapeutic indications* (restrictions, length and specificity, other differences), and for *contraindications, warnings and precautions* (other differences).

3. Results

Products were included in the study if information on the product was available at the websites of both the EMEA and the FDA. Thirty-two products fulfilled the inclusion criteria (Table 2).

3.1. Approval date of marketing authorisation

Twelve products were approved at an earlier date and 21 products later in the EU as compared to the USA. For the 12 products approved at an earlier date, the l average approval time was 599.5 days earlier, the median 299 days and the range was from 3 to 1929 days. For the 20 approved later, the average approval time was 680 days and the median 433 days later and the range was from 51 to 2728 days. For some products, a long period between the marketing authorisations may be explained by the withdrawal of the first submission in order to avoid an official rejection.

Table 2
Trade names of biopharmaceuticals studied

Products A–N	Products P–Z
Aranesp (darbepoetin alfa)	Pegasys (peginterferon alfa-2a)
Avonex (interferon beta 1a)	Prevenar/prevnar (pneumococcal saccharide
Benefix (nonacog alfa)	conjugated vaccine)
Betaferon/betaseron (interferon beta-1b)	Puregon/follistim (follitropin beta)
Cerezyme (imiglucerase)	Rebif (interferon beta-1a)
Fabrazyme (agalsidase beta)	Refacto (moroctocog alfa)
Herceptin (trastuzumab)	Regranex (becaplermin)
Humalog (insulin lispro)	Remicade (infliximab)
Infergen (interferon alfacon-1)	Simulect (basiliximab)
IntronA (interferon alfa-2b)	Somavert (pegvisomant)
Kineret (anakinra)	Synagis (palivizumab)
Kogenate (octocog alfa)	Thyrogen (thyrotropin alfa)
Lantus (insulin glargine)	Twinrix (comb. Hepatitis A and B vaccine)
Neulasta (pegfilgrastim)	Xigris (drotecogin alfa)
Novomix/novolog Mix 70/30 (insulin aspart)	Zenapax (daclizumab)
Novoseven (eptacog alfa)	Zevalin (ibritumomab tiuxetan)
Nutropin Aq (somatropin)	

3.2. Therapeutic indications

The EU guideline [12] requires the definition of the target disease and separation between treatment, prevention and diagnosis. When appropriate, the target population (e.g. a subgroup of patients) should also be defined. In the FDA, the CFR Title 21 [13] describes the meaning of indication more accurately. The staple, however, is that the medicinal product must be indicated for the treatment, prevention, or diagnosis of a recognised disease or condition or an important manifestation of a disease or a condition, or relief of symptoms associated with a disease or syndrome.

In the present study, 31 of the 32 products were indicated for the same diseases both in the EU and in the USA. Only one product (Aranesp) had one additional indication in the EU as compared to US. In order to analyse the regulatory approach to the therapeutic indication(s), restrictions to the given indication(s) as well as specificity of wording were examined (Table 3). The indications were more restricted in the EMEA. The indication of Rebif may be given as an example. The EU SPC requires that the patient has had two or more MS relapses within the last 2 years. Such a requirement is not included in the US PI.

3.3. Contraindications

The EU guideline [12] defines contraindications as situations, where safety reasons must prohibit use of the product. In addition, the guideline mentions that other medicines or classes of medicines that should be avoided for concomitant or consecutive use should also be stated in this section. Pregnancy should be mentioned only if the use of a product is strictly contraindicated. Hypersensitivity to any

Table 3
Comparison of therapeutic indications

Number of the indications	Same	31
	More in the EMEA	1
	Less in the EMEA	0
Number of restrictions for the use	Same	17
	More in the EMEA	11
	Less in the EMEA	4
Specificity of wording	Same	12
	More detailed in the EMEA	8
	Less detailed in the EMEA	12

of the excipients or residues from the manufacturing process may be included as well as any contraindication arising from the presence of a certain excipient. In the US, the contraindications are defined as situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. Theoretical possibilities should not be listed, i.e. if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication [13].

There were major differences in the number of contraindications in the EU SPC and the USA PI (Table 4). Only 12 products had the same number of contraindications (e.g. Synagis and Refacto). As many as 18 products had more (e.g. Avonex and Intron A), and only two (Prevenar and Somavert) had fewer contraindications in the EU. The arithmetical average for contraindications was 2.9 in the SPC and 1.6 in the US PI. The Wilcoxon-test was used for evaluation of differences in numbers of contraindications and a statistically significant difference ($P=0.0002$) was observed. An example of a divergent approach is pregnancy that is more often regarded as a contraindication in the EU. Herceptin may be given as another example, wherein the EU SPC hypersensitivity to any excipients and severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen are contraindications. In the US PI, there are no contraindications. In general, conditions labelled as contraindications in EU SPC were noted as warnings/relative contraindications in the US PI.

3.4. Warnings and precautions

In the EMEA, warnings and precautions describe the relative contraindications and conditions under which the use of the medicinal product could be acceptable, provided that special conditions for use are fulfilled [12]. The FDA requires that under the warnings sections, the labelling shall describe serious adverse reactions and potential safety hazards, limitations in use imposed by them, and steps that should be taken if they occur [13]. The present study shows that 15 products had an equal number of warnings and precautions, although these were not necessarily the same in every case (Table 4), e.g. Herceptin has five warnings in both EU SPC and the US PI: cardiotoxity, analysis of Her-overexpression, long half-life of the product, hypersensitivity, and pulmonary events. The US PI acknowledges cardiotoxicity, analysis of Her-overexpression, and hypersensitivity but not the other EU warnings. Instead, it mentions the interaction with paclitaxel and the presence of benzyl alcohol. Eleven products (e.g. Synagis and Puregon) had more warnings and precautions in the EMEA whereas six (e.g. Novomix and Thyrogen) had fewer than in the corresponding US PIs.The Wilcoxon-test was used for evaluation of differences in numbers of warnings and precautions. According to the test the P-value was 0.0911.

Table 4
Comparison of contraindications, warnings and precautions and adverse reactions

Contraindications	Equal number	12
	More in the EMEA	18
	Less in the EMEA	2
Warnings and precautions	Equal number	15
	More in the EMEA	11
	Less in the EMEA	6
Adverse reactions	Similar presentation	14
	More detailed in the EMEA	3
	Less detailed in the EMEA	15

3.5. Adverse reactions

The term of adverse reaction is used by the US while the term undesirable effect is used in the EU SPC. For ease of communication, the FDA terminology will be used in the present text. The EMEA requires that this section should list all adverse effects that are at least possibly related to the use of the product by frequency and organ system [12]. For the FDA, adverse reactions may be categorised by organ system, by severity of the reaction, by frequency, or by toxicological mechanism, or by a combination of these, as appropriate [13]. Fourteen of the products included in this study had the same degree of detail for adverse reactions (e.g. Cerezyme) and 15 products had less detailed presentation of adverse events in the EU SPC (e.g. Lantus) (Table 4). Only three additional products had more detailed information (e.g. Nutropin Aq), including crude frequencies for both the product and the comparator, in the EU SPC. No attempt was made to compare the EU SPC and the US with regard to the individual adverse effects.

3.6. Pregnancy and lactation

Instructions for use during pregnancy were not consistent between the continents as only 17 products had similar labelling requirement in the FDA and the EMEA (Fig. 1). In general, the EU SPCs imposed stricter restrictions. Furthermore, the use during pregnancy was contraindicated for nine products in EU SPCs and only for two products (Thyrogen and Puregon) in the US PI.

The approach to lactation was also more conservative in the EU SPCs as compared to US PIs. Lactation was contraindicated with three products (Pegasys, Simulect and

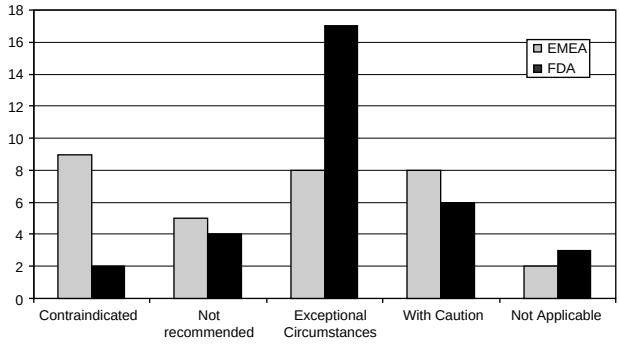

Fig. 1. Differences in the approaches to the pregnancy in marketing approval issued by the EMEA and the FDA.

Zenapax) by the EU SPC, but not in any product by the FDA (Fig. 2). All of these three products were stated as 'not recommended' by the FDA. Lactation was not recommended for six such products (Aranesp, Fabrazyme, Kineret, Rebif, Regranex and Thyrogen) by the EMEA, with which lactation was allowed 'with caution' in the FDA.

3.7. Pharmacodynamics and efficacy data

According to the guideline [12], the EU SPC describes data on the pharmacotherapeutic group, mechanism of action (if known) and pharmacodynamic effects. In general, no information on clinical trial data are expected here. Exceptionally, results on clinically relevant endpoints and the main characteristics of the patient population can be mentioned. Clinical data are mandatory for products approved under exceptional circumstances. According to the US policy [13], the clinical pharmacology section should contain a concise factual summary of the clinical pharmacology and actions of the drug in humans. The summary may include information based on in vitro and/or animal data, pharmacokinetic information that is essential to safe and effective use of drug and under certain circumstances data that demonstrate activity or effectiveness in in vitro or animal tests and that have not been shown by adequate and well-controlled clinical studies. A detailed description of well-controlled pivotal studies is allowed in the 'Clinical Studies' section of the US PI [13].

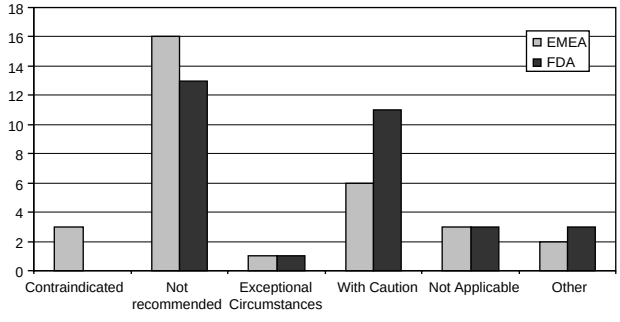

Fig. 2. Differences in the approaches to the lactation in marketing approval issued by the EMEA and the FDA.

Only four products (Neulasta, Pegasys, Betaferon and Zevalin) had a similar level description of pharmacodynamics/clinical results, whereas 28 products had a shorter description of clinical data in the EU SPC. The EU SPC aims to present only core clinical data that gives the prescriber the essential information on the patient population, methods and efficacy outcome, including the size of the treatment effect. Sometimes data from different studies were either pooled across different pivotal studies or presented side by side. Furthermore, the clinical data in the EU SPC were restricted to the primary efficacy endpoints with absolute and relative changes. In contrast, the US PI had generally a detailed description of the clinical results in a tabular form.

3.8. Posology and paediatric use

The EU guideline [12] requires that the dosage has to be clearly specified for each method/route of administration and for each indication. In the US [13], this part of labelling should contain the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established. The section should also state the intervals recommended between doses, the optimal method of titrating dose, the usual duration of treatment, and any modification of dosage needed in special patient populations.

In this study, 25 products had the same and six had different posology. The differences were often minor. For example, the loading dose of Somavert is 80 mg in the EU SPC and 40 mg in the US PI. Somavert has a different loading dose but the same maintenance dose, FDA recommends a slightly different dosage as compared to EMEA for Nutropin. Somewhat more significant differences include the following: Twinrix has an accelerated vaccination schedule in EU in addition to the standard schedule. The dosing of the topically administered Regranex is very detailed in the US PI whereas the EU EPC allows more flexibility. For Aranesp, the EU SPC and US PI recommend the same dose but the treatment initiation and duration is based on different plasma haemoglobin levels. For some products, one agency permitted dose titration whereas the other preferred a fixed lower dose. The US PI gives a more systematic information on special groups whereas in the EU, only the use in children is regularly mentioned. Obviously, the use in some special populations is often not critical for biological products and therefore often omitted in the EU SPC.

Recommendation for paediatric use was the same for 25 products. For two products (Lantus and Neulasta), the data on safety and efficacy were deemed insufficient in the EU SPC but not in the US PI and for two other products (Thyrogen and Twinrix), the situation was the opposite. In three cases (Pegasys, Rebif and Betaferon), paediatric use was not permitted in the EU SPC while the US PI stated that the product has not been studied in the paediatric population.

4. Discussion

The present study suggests that for the 32 biopharmaceuticals examined, the EU SPC contained more detailed instructions to the prescriber, including the positioning of the product with regard to the stage of the disease and to other therapies. Furthermore, the approach to safety information, notably to contraindications and warnings appeared to be more conservative in the EU SPC.

Taking into account the fact that the structure and content of the SPC and PI are based on different local guidelines, the differences between the EU SPC and the USA PI were not striking. This might imply that the scientific evaluation of benefit/risk by the EMEA and the FDA is fairly similar. However, such a conclusion is premature because public information on applications that one regulatory authority approved but the other found non-approvable are not available. In our opinion, such data should be available for public scrutiny in order to increase awareness of the critical areas of benefit/risk assessment in the EMEA and the FDA.

There are certain limitations to the study, which should also be noted. The analysis was based on the updated product information retrievable from the home pages of the EMEA and the FDA. Thus, the different timing of regulatory approval is unlikely to explain the observed differences. The assessment of some items required subjective assessment. For example, the assessment of restrictions to the therapeutic indications was not based on simple counting but on an estimation of the impact of the restrictions on both the size of the potential market and on the willingness of the physicians to prescribe (Table 5).

The following discussion on the reasons for the observed differences between the EU SPC and the US PI is focused on the following points: interface between the product labelling on one side and the medical praxis, including the positioning of the new products, risk management of new biotechnology-derived medicinal products, and the control of the promotion of medicinal products, on the other side. Furthermore, some differences may originate from the characteristics of the European and US regulatory systems as such. Finally, we emphasise the fact that clinical development plans based on requirements in one region may not lead to an optimal labelling in the other region

The observed differences may reflect differences in the goals of the regulators with regard to the product labelling. A general observation was that the EU SPC is more detailed in its instructions to the prescriber in the sections describing the clinical use of the product. The FDA generally has less restrictive indications and less contraindications and warnings but presents safety and efficacy data in a more detailed and less digested form. Thus, the prescriber is given more freedom in interpreting data and in the clinical use of the product. Detailed instructions to the prescriber might be regarded as *interference in the medical praxis*, which is beyond the jurisdiction of the drug regulatory agencies. However, this issue should not be over-emphasised since the prescribers will receive additional guidance from other sources such as learned societies, insurance companies, health maintenance organisations and reimbursement authorities. This guidance will usually go much further than the information in the EU SPC and the US PI.

The approach to safety information, notably to contraindications and warnings, was clearly more conservative in the EU SPC. The contraindications of the EU SPC were often presented as warnings/relative contraindications in the USA PI. In spite of this, the EU SPC often contained more warnings. This difference may reflect the approaches to *risk*

Table 5
An example of the analysis of the indication and its restrictions

	Therapeutic indication		Restrictions	
	EU SPC	US PI	EU SPC	US PI
Simulect (basiliximab)	Prophylaxis of acute organ rejection	Prophylaxis of acute organ rejection	In de novo allogeneic renal transplantation And is to be used concomitantly with ciclosporin for microemulsion- and corticosteroid-based immuno-suppression In patients with panel reactive antibodies less than 80%.	Renal transplantation when used As part of an immunosuppressive regimen that includes cyclosporine and corticosteroids
Comment	The same indication		EU SPC more restrictive: only in de novo patients without a high risk	
Kineret (anakinra)	Treatment of the signs and symptoms of rheumatoid arthritis	Reduction in signs and symptoms of moderately to severely active rheumatoid arthritis	In combination with methotrexate In patients with an inadequate response to methotrexate alone	In patients 18 years of age Who have failed one or more disease modifying antirheumatic drugs
Comment	Practically the same indication		EU SPC more restrictive: only combination treatment, the age restriction is in the posology section	

management of new medicinal products by the two agencies. The EMEA is prone to use a conservative labelling and limited prescription as a risk management tool for new active substances, whereas the US risk management systems put more emphasis on other elements. Some differences, such as more frequent inclusion of pregnancy to contraindications may be associated with legal, religious and liability issues in the EU Member States.

Therapeutic indications will govern the clinical use of a product and, thus, the size of the market. Promotion of non-licensed indications is prohibited and the off-label use may expose the prescriber for liability issues. While the number of therapeutic indications was usually the same in the EU and in the USA, therapeutic indications granted in the EU tended to be more restricted as compared to the USA. The use of a product in a particular disease may be restricted in several ways, e.g. by allowing the use only in a subset of a disease, by requiring specific diagnostic procedures such as histological evidence of the disease, or by mandating strict monitoring procedures of the treatment. A typical difference between the EMEA and FDA is the approach to *positioning of the new product towards the existing treatment options* in the EU. The EU regulators favour the use of active-controlled clinical studies in addition to the placebo-controlled studies. Such studies will help in the evaluation of the benefit/risk of a new therapy. It is generally accepted that active-controlled studies are generally essential for the prescriber who wishes to select the most appropriate treatment for a particular patient. For the time being, there is no consensus as when such studies should be carried out—pre- or post-licensing.

The description of clinical trial data, including efficacy, in the USA PI is very detailed. Thus, the prescriber has the possibility for his/her own judgement on the clinical performance of the product. Another benefit is to reach an agreement between the marketing authorisation holder and the regulators as *how to present the benefits of the product in the promotional material*. According to the present EU guideline, the SPC should normally contain data on pharmacodynamics only. However, omitting quantitative information on the clinical benefits in the SPC will leave room for promotional interpretations. Therefore, most recent EU SPCs have a description of the pivotal clinical trials, mainly the patient populations and the absolute and relative magnitude of the treatment effect.

The different conditions for marketing authorisation in the EU and the US may also be due to *clinical development plans* of the companies that are often designed to satisfy the regulatory requirements in the US. In contrast to the EU, the clinical development in the US requires regular contacts to the FDA in order to ensure the compliance with local regulations and regulatory standards. Thus, European regulators often have to review data from development programmes that are tailored for the FDA. It is obvious that such a dossier will meet more questions when submitted to the EU. The recent efforts to increasing communication between the two regulatory authorities on product-specific regulatory guidance may diminish differences in the outcome of the regulatory review, including product information [14].

Differences between the EU and US are to be expected due to characteristics of *the responsible regulatory agencies and procedures*; EMEA is co-ordinating a network of national experts in the EU whereas the FDA operates a fully centralised licensing system. Thus, there are more experts and regulators contributing to the review of the dossiers in the EU centralised system where two review teams from different member states are responsible for the initial assessment followed by peer review of experts in the other EU member states. Under these circumstances, compromises to settle divergent views may lead to a conservative approach that has an impact on product information in the EU SPC. However, the reasons for differences may have much deeper roots in the diversity of circumstances within the EU, including characteristics of the health care systems and the legal frameworks and as well as cultural, moral and religious values of the societies.

These results may represent a signal of a more conservative regulatory environment in the EU as compared to the USA. This may reflect a general philosophical difference between the Europe and the USA as how to balance the needs of public health on one side, and the interests of pharmaceutical industry, on the other hand. In spite of increasing harmonisation of regulatory requirements, the developers of medicinal products for global market should understand the prevailing differences between the regulatory approaches and design the clinical development programmes accordingly.

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