

Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union

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BIOLOGICALS, DEFINED AS PRODUCTS of which the active substance is produced by or extracted from a biological source, represent an important and growing part of the therapeutic arsenal.¹ In the United States, the first biological, recombinant insulin, was approved in October 1982.² Since then, more than 250 biologicals, including recombinant (blood) products, monoclonal antibody-based products, and recombinant vaccines have been approved by regulatory authorities.³ Between 2003 and 2006, biologicals represented 24% and 22% of all new chemical entities approved by the US and EU regulatory authorities, respectively.⁴ Sales of biotech products in the United States showed an annual growth rate of 20% between 2001 and 2006 compared with 6% to 8% in the pharmaceutical market.⁵

Knowledge of a new drug is incomplete at the time of approval, especially with reference to its safety profile, due to a variety of factors including constraints in the sample size and the

For editorial comment see p 1939.

Context Biologicals are a relatively new class of medicines that carry specific risks (eg, immunogenicity). However, limited information is available on the nature and timing of safety problems with their use that were identified after approval.

Objective To determine the nature, frequency, and timing of safety-related regulatory actions for biologicals following approval in the United States and/or the European Union.

Design and Setting Follow-up of a group of biologicals approved in the United States and/or European Union between January 1995 and June 2007. Vaccines, allergenic products, and products for further manufacture and transfusion purposes were excluded.

Main Outcome Measures Nature, frequency, and timing of safety-related regulatory actions defined as (1) dear healthcare professional letters (United States) and direct healthcare professional communications (European Union), (2) black box warnings (United States), and (3) safety-related marketing withdrawals (United States and European Union) issued between January 1995 and June 2008.

Results A total of 174 biologicals were approved (136 in the United States and 105 in the European Union, of which 67 were approved in both regions). Eighty-two safety-related regulatory actions (46 dear healthcare professional letters, 17 direct healthcare professional communications, 19 black box warnings, and no withdrawals) were issued for 41 of the 174 different biologicals (23.6%). The probability of a first safety-related regulatory action, derived from Kaplan-Meier analyses, was 14% (95% confidence interval [CI], 9%-19%) 3 years after approval and 29% (95% CI, 20%-37%) 10 years after approval. Biologicals first in class to obtain approval had a higher risk for a first safety-related regulatory action compared with later approved products in that class (12.0/1000 vs 2.9/1000 months, respectively; hazard ratio, 3.7 [95% CI, 1.5-9.5]). Warnings mostly concerned the classes general disorders and administration site conditions, infections and infestations, immune system disorders and neoplasms benign, malignant, and unspecified.

Conclusions The nature of safety problems identified after approval for biologicals is often related to the immunomodulatory effect (infections). Because the biologicals first to be approved in a class were more likely to be subjected to regulatory action, close monitoring is recommended.

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design of randomized controlled trials.^{6,7} Although this also applies to small molecules, biologicals carry specific risks. In contrast to small molecules, which are synthesized chemically, biologicals are derived from living sources (eg, humans, animals, cells, and microorganisms). The production and purification process of biologicals is more complex, involving numerous steps with the risk of influencing the characteristics of the end product at any single step in the production cascade.^{8,9} Small differences and changes in the production process can therefore have major implications on the safety profile of biologicals. For example, the incidence of pure red cell aplasia in patients treated with recombinant human epoetin, an extremely rare complication induced by antibodies, was elevated in patients taking one particular formulation of recombinant human epoetin in which human serum albumin was replaced with polysorbate 80 and glycine.^{10,11} However, the exact mechanism underlying the increased risk of pure red cell aplasia after the formulation change is not yet fully understood.¹² The risk of contamination with pathogens by the donor is another problem related to the production process (eg, for products extracted from human blood or plasma).¹³

Biologicals are specifically prone to the induction of immunogenicity. In many cases, the consequence of immunogenicity is not clinically relevant. However, in some cases immunogenicity can lead to loss of efficacy of the drug or, even worse, lead to autoimmunity to endogenous molecules. There can be a major clinical impact if a natural protein with essential biological activity is neutralized by antibody formation.^{8,10,14,15}

The predictability of preclinical data to humans is limited for biologicals due to the species-specific action and immunogenic properties in animals.⁹ A recent striking example of this has been the occurrence of serious adverse events in healthy volunteers participating in a phase 1 clinical study of TeGenero's TGN1412, a CD28 agonist monoclonal antibody. The observed cytokine

storm following infusion had not been observed in the preclinical studies of TGN1412.¹⁶ To obtain valuable results from the preclinical (toxicology) studies, a relevant test animal should not only be selected based on pharmacological activity and low immunogenicity, but suitable pharmacokinetic properties also should be taken into account.^{17,18} In some cases, the preclinical program is further complicated by a complex pharmacodynamic-pharmacokinetic relationship that can be illustrated by the delayed pharmacodynamic effect of peginterferon interleukin 2, which becomes apparent long after the drug has disappeared from the blood compartment. Another complicating factor is the occurrence of bell-shaped response curves often seen in animals, especially with cytokines, in which the desired effect disappears after an increase of the dose.¹⁹ Biologicals mainly act extracellularly and toxicity is often attributed to an exaggerated pharmacology,¹⁸ which can be illustrated by the occurrence of serious infections due to the immunomodulatory function of many biologicals (eg, monoclonal antibodies and interferons).²⁰⁻²²

As shown in previous studies, the use of drugs in the postapproval real-world setting can lead to the identification of important safety problems, which may even result in the withdrawal of drugs from the market.^{23,24} Because biologicals carry specific risks, and limited information is available on the nature and timing of safety-related regulatory actions issued after approval for biologicals, our study examines the nature of the safety-related regulatory actions issued for biologicals and determines the probability of a safety-related regulatory action being issued after approval. Based on the immunomodulatory function of many biologicals, it is expected that an important part of the warnings for biologicals are related to this characteristic. In addition, within the group of biologicals, differences in the risk of safety-related regulatory actions (eg, between mechanistic classes) also are studied.

METHODS

Biologicals

This study included biological medicinal products (biologicals) approved in the United States and/or the European Union between January 1995 and June 2007. Biologicals were defined according to the European Medicines Agency (EMA).¹ The same active substances marketed by different pharmaceutical companies and biosimilars were included in the study as separate biologicals.

For the United States, the study included biologicals approved by the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER; data available from January 1996 onward). The information was obtained from the Web sites of CBER (<http://www.fda.gov/cber>) and CDER (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda>), respectively. Biologicals licensed under the same application number were included only once. Within the European Union, biologicals granted a marketing authorization were identified from the European public assessment reports for authorized medicinal products for human use. All information was retrieved from the Web site of the EMA (<http://www.emea.europa.eu>).

Biologicals with an extension of indication during the study period, vaccines, allergenic products (allergen patch tests and allergenic extracts), biological products for further manufacture, and biological products for transfusion purposes and maintenance of circulating blood volume were excluded.

Biologicals were classified in therapeutic classes according to the Anatomical Therapeutic Chemical classification system (<http://www.whocc.no/atcddd>), and were classified in the mechanistic classes of antibodies (including monoclonal antibodies), cytokines, enzymes, growth factors, hormones, interferons, receptors, and others/various. Monoclonal antibodies were further classified into murine, chimeric, and humanized.^{25,26}

Safety-Related Regulatory Actions

Safety-related regulatory actions were defined as (1) written communications to health care professionals (dear healthcare professional letters [DHPLs] in the United States and direct healthcare professional communications [DHPCs] in the European Union), (2) postapproval black box warnings (United States only), and (3) market withdrawals due to safety reasons (United States and European Union). Safety-related regulatory actions were collected between January 1995 and June 2008, which ensured at least 1 year of follow-up for each of the biologicals being studied.

Dear healthcare professional letters were identified from MEDWATCH from 1996 onward (<http://www.fda.gov/medwatch>). Direct healthcare professional communications were identified from the Web site of the Medicines Evaluation Board in the Netherlands (<http://www.cbg-meb.nl>) and the European public assessment reports of the EMEA. The date of the letter was used as the date of the safety-related regulatory action. Letters not including safety warnings and follow-up letters of previously issued letters containing no new safety information were excluded.

Postapproval black box warnings were identified from the labels available from the Web sites of CDER, CBER, MEDWATCH, and the marketing authorization holder and announcements posted on the MEDWATCH Web site. The latest approved label of every biological available from CDER was searched for a black box warning. When a black box warning was identified from the latest approved label, previously approved labels were checked to identify the date the black box warning was added, which was cross-checked with the information from MEDWATCH. Labels that could not be retrieved from CDER were retrieved from CBER, MEDWATCH, and/or the marketing authorization holder. The date of the black box warning stated on the Web sites of CDER, CBER, or MEDWATCH was included in the analysis. When the

exact date of the black box warning could not be identified, the latest possible date the black box warning was issued was included in the analysis. No label could be retrieved for 1 biological, and this biological was excluded from the analysis of black box warnings.

Drug withdrawals for safety reasons were identified from MEDWATCH, CDER, and the European public assessment reports listed on the EMEA Web site. The date of the decision was used in the analysis.

Source and Nature of the Safety Information

The source of the safety-related regulatory action described in the communications to health care professionals was collected and classified as postapproval reports (including both sponta-

neous reports as well as pharmacoepidemiological studies and registries), clinical trial data, a combination of postapproval reports and clinical trial data, others, or unknown. Because information on the source of the safety-related regulatory action is normally not included in a black box warning, these warnings were excluded from this part of the analysis, in which the source of the safety-related regulatory action was studied.

The nature of the safety information was coded according to the Medical Dictionary for Regulatory Authorities version 9.1. The primary reasons for the dissemination of the safety-related regulatory action were included in the analysis. Safety information was encoded using 5 levels: lower-level term, preferred term, higher-level term, high-level group term, and

Table 1. Biologicals Approved Between January 1995 and June 2007 and Classified by Therapeutic Class (N=174)

	No. (%) of Biologicals Approved		P Value
	United States (n = 136)	European Union (n = 105)	
Alimentary tract and metabolism			
Insulins and analogues	10 (7.4)	24 (22.9)	<.001
Other alimentary tract and metabolism products	6 (4.4)	7 (6.7)	.44
Blood and blood-forming organs			
Antithrombotic agents	13 (9.6)	9 (8.6)	.79
Vitamin K and other hemostatics	12 (8.8)	9 (8.6)	.95
Other antianemic preparations	1 (0.7)	4 (3.8)	.10
Other hematological agents	4 (2.9)	0	NA
Cardiovascular system	1 (0.7)	0	NA
Dermatologicals	1 (0.7)	1 (1.0)	.85
Genitourinary systems and sex hormones			
Gonadotrophins and other ovulation stimulants	7 (5.1)	4 (3.8)	.62
Systemic hormonal preparations, excluding sex hormones and insulins			
Anterior pituitary lobe hormones and analogues	13 (9.6)	4 (3.8)	.08
Pancreatic hormones	2 (1.5)	0	NA
Calcium homeostasis	2 (1.5)	2 (1.9)	.79
Anti-infectives for systemic use			
Immunoglobulins	15 (11.0)	2 (1.9)	.01
Antineoplastic and immunomodulating agents			
Cytokines and immunomodulators	9 (6.6)	12 (11.4)	.19
Immunosuppressive agents	12 (8.8)	11 (10.5)	.67
Other antineoplastic agents	8 (5.9)	5 (4.8)	.70
Musculoskeletal system	2 (1.5)	3 (2.9)	.45
Respiratory system	3 (2.2)	1 (1.0)	.45
Sensory organs	2 (1.5)	1 (1.0)	.72
Others/various	13 (9.6)	6 (5.7)	.27

Abbreviation: NA, data not applicable.

system organ class, but only the system organ class level was used in the analysis.

Data Analysis

The number of biologicals classified at the Anatomical Therapeutic Chemical level in the United States and European Union were compared by the χ^2 test. The mean time to a safety-related regulatory action was calculated by summing the times between approval and a warning and dividing by the total number of safety-related regulatory actions issued. The incidence of safety-related regulatory actions was calculated as a simple proportion. Kaplan-Meier survival curves were used to estimate the probability of the occurrence of a safety-related regulatory action for the total group of biologicals (those approved in either the United States or European Union), and for the subgroups (those approved in the European Union and United States separately, depending on the safety-related regulatory action of interest). For biologicals that acquired multiple safety-related regulatory actions, only the first regulatory action was included in the analysis.

Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were calculated using the Cox proportional hazards model. The HRs were calculated to assess if the first biological approved in a (new) chemical, pharmacological, and therapeutic subgroup, as defined by the Anatomical Therapeutic Chemical classification system, had a higher risk of a safety-related regulatory action compared with biologicals approved at a later stage.

To evaluate if experience with biologicals (those approved at a later point in time) might influence the number of safety-related regulatory actions, 2 time frames were constructed that included biologicals approved between January 1995 and June 2001 (6.5 years) and between July 2001 and June 2007 (6 years). The HRs also were calculated to compare the risk of safety-related regulatory actions issued for different mechanistic classes of biologicals

as described previously. Hormones were used as the reference group because there is long-term, extensive experience with hormones within the group of biologicals, and hormones are often imitations of naturally occurring substances.²⁶ For the subgroups of biologicals approved in the United States and European Union, the time-to-event distributions of DHPLs issued in the United States and DHPCs issued in the European Union were compared by HRs, which included a variance adjustment to account for statistical independence.

For a subgroup of biologicals approved in both the United States and European Union, the nature and timing of the safety-related regulatory action were compared descriptively. When a safety-related regulatory action was issued for a biological not approved in the other region at the time of the regulatory action, this regulatory action was excluded. The timing of a safety-related regulatory warning was classified (1) in the United States first (European Union >2 months later), (2) in the European Union first (United States >2 months later), and (3) in both the United States and European Union within a period of 2 months.

All statistical analyses were conducted by using the statistical software package SPSS version 14 (SPSS Inc, Chicago, Illinois) and S-PLUS version 6.2 (Insightful Corp, Seattle, Washington). All hypotheses were tested using 2-sided tests with an α level of .05. All analyses were unadjusted because the objective of this study was descriptive and not etiologic in nature.

RESULTS

A total of 174 biological medicinal products obtained approval between January 1995 and June 2007; this comprised 136 biologicals approved in the United States and 105 in the European Union, of which 67 biologicals obtained approval in both regions during the study period (TABLE 1).

The differences between the number of approved biologicals in the

United States and European Union was mostly explained by differences in the Anatomical Therapeutic Chemical classes of insulins and analogues ($P < .001$), other antianemic preparations ($P = .10$), anterior pituitary lobe hormones and analogues ($P = .08$), and immunoglobulins ($P = .01$).

During the period under review, 82 safety-related regulatory actions were issued for 41 of the 174 biologicals (23.6%). These included 46 DHPLs (TABLE 2), 17 DHPCs (TABLE 3), and 19 black box warnings (TABLE 4). No biologicals were withdrawn due to safety reasons. The mean time to elicit a safety-related regulatory action was 3.7 years and 70.7% of the safety-related regulatory actions were issued within 5 years after approval. The Kaplan-Meier probability of a biological requiring its first safety-related regulatory action was 14% (95% CI, 9%-19%) 3 years after approval and 29% (95% CI, 20%-37%) 10 years after approval.

Biologicals that were the first to be approved in their chemical, pharmacological, and therapeutic subgroup had a significantly higher risk for the occurrence of its first safety-related regulatory action compared with later approved products (HR, 3.7; 95% CI, 1.5-9.5). When the first approved products also included biologicals approved in a chemical, pharmacological, and therapeutic subgroup in which small molecules already had been approved, a significant increased risk for the first safety-related regulatory action was found as well (HR, 2.3; 95% CI, 1.1-4.8) (TABLE 5). Biologicals approved between July 2001 and June 2007 had a nonsignificantly higher risk for their first safety-related regulatory action compared with biologicals approved between January 1995 and June 2001 (HR, 1.5; 95% CI, 0.8-2.8) (Table 5).

A significantly higher risk for a first safety-related regulatory action compared with hormones was found for antibodies (HR, 12.1; 95% CI, 3.6-40.9), cytokines (HR, 17.3; 95% CI, 3.5-86.1), growth factors (HR, 8.2; 95% CI, 1.4-49.1), interferons (HR, 7.3; 95% CI, 1.6-32.8), and receptors (HR, 34.2; 95%

Table 2. Biologicals With a Dear Healthcare Professional Letter (DHPL) in the United States

Class of Biological	Active Substance	Drug Name	Drug Approval Date	Warning	Time to DHPL, y
Antibodies	Adalimumab	Humira	December 31, 2002	Serious infections in combination with anakinra, hypersensitivity reactions, hematologic events	1.8
	Basiliximab	Simulect	May 12, 1998	Severe acute hypersensitivity reactions	2.4
	Bevacizumab	Avastin	February 26, 2004	Arterial thromboembolic events	0.5
				Reversible posterior leukoencephalopathy syndrome Tracheoesophageal fistula	2.5 3.1
	Cetuximab	Erbix	February 12, 2004	Hypomagnesemia, infusion reactions	1.6
	Daclizumab	Zenapax	December 10, 1997	Increased mortality in a study, hypersensitivity reactions	5.6
	Efalizumab	Raptiva	October 27, 2003	Immune-mediated hemolytic anemia, serious infections, thrombocytopenia	1.7
	Ibritumomab tiuxetan	Zevalin	February 19, 2002	Severe cutaneous and mucocutaneous reactions	3.6
	Infliximab	Remicade	August 24, 1998	Adverse events due to antibodies	0.2
				Tuberculosis and other opportunistic infections	3.1
				Worsening heart failure	3.2
				Malignancies (lymphoma)	6.1
				Hepatotoxicity	6.3
	Natalizumab	Tysabri	November 23, 2004	Progressive multifocal leukoencephalopathy	0.4
				Progressive multifocal leukoencephalopathy Hepatotoxicity	1.6 3.2
	Normal immunoglobulin	Venoglobulin	January 10, 1997	Renal dysfunction and/or acute renal failure	1.8
	Palivizumab	Synagis	June 19, 1998	Anaphylaxis	4.4
	Ranibizumab	Lucentis	June 30, 2006	Stroke	0.6
	Intravenous RhoD immunoglobulin	WinRho SDF Liquid	March 21, 2005	Intravascular hemolysis in patients with idiopathic thrombocytopenic purpura; potential interference with blood glucose measurement	0.7
Rituximab	Rituxan	November 26, 1997	Severe infusion-related adverse events	1.0	
			Hepatitis B reactivation with related fulminant hepatitis	6.6	
Technetium fanolesomab	Neutrospec	July 2, 2004	Cardiopulmonary events	1.4	
Trastuzumab	Herceptin	September 25, 1998	Hypersensitivity reactions, infusion reactions, pulmonary events	1.6	
			Cardiotoxicity	6.9	
Cytokines	Denileukin diftitox	Ontak	February 5, 1999	Visual loss	7.1
	Oprelvekin (interleukin-11)	Neumega	November 25, 1997	Papilledema	3.7
Enzymes	Drotrecogin alfa	Xigris	November 21, 2001	Mortality in patients with single organ dysfunction and recent surgery	3.2
				Central nervous system bleeding	3.4
	Eptacog alfa	Novoseven	March 25, 1999	Thrombotic and thromboembolic adverse events	6.7
	Nesiritide	Natrecor	August 10, 2001	Increased 30-d mortality	3.7
Streptokinase	Streptase	November 15, 1997	Adverse events during off-label use; hypotension, hypersensitivity reactions, apnea, bleeding	2.2	
Growth Factors	Beclapernin	Regranex	December 16, 1997	Increased risk of mortality secondary to malignancy	10.5
Hormones	Darbepoetin alfa	Aranesp	September 17, 2001	Thrombotic events, increased mortality, tumor growth potential	3.3
				Pure red cell aplasia and severe anemia associated with neutralizing antibodies	4.1
				Increased mortality in a trial	5.4
	Insulin human inhalation powder	Exubera	January 27, 2006	Primary lung malignancies	2.2
Somatotropin	Genotropin	August 24, 1995	Increased mortality in a trial	2.2	
			Fatalities	7.8	
Interferons	Interferon beta-1a	Avonex	May 17, 1997	Antibody formation Hepatic injury	5.8 7.8
Others/Various	Danaparoid sodium	Orgaran	December 24, 1996	Epidural or spinal hematomas	1.0
Receptors	Alefacept	Amevive	January 30, 2003	Contraindication in patients with human immunodeficiency virus; alefacept might accelerate disease progression or increase complications of disease	2.7
	Etanercept	Enbrel	November 2, 1998	Serious infections including sepsis	0.5
Central nervous system disorders, pancytopenia				1.9	

CI, 5.6-211.1). Compared with humanized monoclonal antibodies, chimeric monoclonal antibodies had a nonsignificantly higher risk (HR, 2.9; 95% CI, 0.9-9.9) and murine monoclonal antibodies had a lower risk (HR, 0.2; 95% CI, 0.03-0.7) for a first safety-related regulatory action (Table 5).

The safety-related regulatory actions issued for biologicals mostly concerned the system organ classes of general disorders and administration site conditions (26.8% of 82), infections and infestations (22%), immune system disorders (15.9%), and neoplasms benign, malignant, and unspecified (12.2%) (Tables 2-4). A quantitative description of the frequency of each type of safety-related regulatory action is shown in TABLE 6.

The 46 DHPLs, 17 DHPCs, and 19 black box warnings related to safety were issued for 30 (22.1%), 11 (10.5%), and 17 (12.6%) different biologicals, respectively. After 10 years, the probability of a first DHPL was 26% (95% CI, 17%-34%); DHPC, 13% (95% CI, 5%-20%); and black box warning, 17% (95% CI, 8%-26%) (FIGURE). Communications to health care professionals were more frequently issued in the United States com-

pared with the European Union (HR, 3.0; 95% CI, 1.2-7.6).

The sources of the safety-related regulatory actions described in DHPLs were postapproval reports (n=18; 39.1%), clinical trial data (n=16; 34.8%), a combination of postapproval reports and clinical trial data (n=9; 19.6%), others (n=2; 4.3%), and unknown (n=1; 2.2%). The sources of the safety-related regulatory actions described in DHPCs were postapproval reports (n=9; 52.9%), clinical trial data (n=5; 29.4%), combination of postapproval reports and clinical trial data (n=1; 5.9%), others (n=1; 5.9%), and unknown (n=1; 5.9%).

Sixty-one safety-related regulatory actions were issued for the subgroup of 67 biologicals approved in both the United States and European Union within the study period. Five safety-related regulatory actions issued in the United States were excluded because the biological was not approved in the European Union at the time of the regulatory action. Nine safety-related regulatory actions issued in both regions involved the same nature (35 were issued only in the United States and 8 were issued only in the European Union). Of

the 9 safety-related regulatory actions issued in both regions, 6 were issued in both regions within 2 months (1 was issued first in the United States and 2 were issued first in the European Union).

COMMENT

The experience with drugs in actual clinical practice complements that of clinical trials and helps to expand the knowledge of the safety profile of drugs.^{7,23,24} Biologicals are a relatively new class of drugs and the expected safety-related regulatory actions issued in the system organ class of infections and infestations relating to the immunomodulatory effect of many of the biologicals was confirmed by the present study. The safety-related regulatory actions issued in the system organ class of general disorders and administration site conditions can be partly explained by the infusion reactions occurring after the parenteral route of administration, which is the mode of administration for most biologicals. A more in-depth evaluation of the mode of action of biologicals might have predicted some safety problems during the developmental phase.

Table 3. Biologicals With a Direct Healthcare Professional Communication (DHPC) in the European Union

Class of Biological	Active Substance	Drug Name	Drug Approval Date	Warning	Time to DHPC, y
Antibodies	Alemtuzumab	MabCampath	July 6, 2001	Cases of death related to infections	6.6
	Bevacuzimab	Avastin	January 12, 2005	Tracheoesophageal fistula	2.3
	Infliximab	Remicade	August 13, 1999	Tuberculosis	1.4
				Worsening heart failure	2.2
				Infections including tuberculosis; contraindication: heart failure	2.5
				Hepatosplenic T-cell lymphoma	6.8
Rituximab	Mabthera	June 2, 1998	Cytokine release syndrome	0.5	
			Progressive multifocal leukoencephalopathy	8.8	
Trastuzumab	Herceptin	August 28, 2000	Cardiotoxicity in combination with anthracyclines and need for cardiac monitoring	1.7	
Cytokines	Anakinra	Kineret	March 8, 2002	Serious infections and neutropenia in combination with etanercept	0.9
Enzymes	Lepirudin	Refludan	March 13, 1997	Fatal anaphylactic reactions	5.6
Growth Factors	Dibotermis alfa	Inductos	November 9, 2002	Postoperative edema at application site	1.9
				Implant site fluid collections	4.5
Hormones	Insulin human inhalation powder	Exubera	June 18, 2008	Primary lung carcinoma	2.4
Others/Various	Botulinum toxin	Neurobloc	March 14, 2001	Muscle weakness, dysphagia, aspiration	6.3
Receptors	Etanercept	Enbrel	February 3, 2000	Blood dyscrasia (pancytopenia, aplastic anemia)	0.7
				Serious infections and neutropenia in combination with kineret	3.0

Table 4. Biologicals With a Black Box Warning (BBW) in the United States

Class of Biological	Active Substance	Drug Name	Drug Approval Date	Warning	Time to BBW, y
Antibodies	Cetuximab	Erbix	February 12, 2004	Cardiopulmonary arrest	2.0
	Gemtuzumab ozogamicin	Mylotarg	May 17, 2000	Hypersensitivity reactions including anaphylaxis, infusion reactions, pulmonary events; hepatotoxicity	0.8
	Ibritumomab tiuxetan	Zevalin	February 19, 2002	Severe cutaneous and mucocutaneous reactions	3.6
	Infliximab	Remicade	August 24, 1998	Risk of infections Hepatosplenic T-cell lymphomas	3.5 7.7
	Natalizumab	Tysabri	November 23, 2004	Progressive multifocal leukoencephalopathy	1.5
	Omalizumab	Xolair	June 20, 2003	Anaphylaxis	4.0
	Rituximab	Rituxan	November 26, 1997	Fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions Progressive multifocal leukoencephalopathy	8.2 9.2
	Trastuzumab	Herceptin	September 25, 1998	Infusion reactions, pulmonary toxicity	3.2
Cytokines	Oprelvekin (interleukin 11)	Neumega	November 25, 1997	Allergic reactions including anaphylaxis	4.8
Enzymes	Laronidase	Aldurazyme	April 30, 2003	Life-threatening anaphylactic reactions	5.0
Growth Factors	Beclapernin	Regranex	December 16, 1997	Increased risk of mortality secondary to malignancy	10.5
Hormones	Darbepoetin alfa	Aranesp	September 17, 2001	Increased mortality, cardiovascular events, thromboembolic events, tumor progression	5.5
Interferons	Interferon alfacon	Infergen	October 6, 1997	Fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders	5.1
	Peginterferon alfa-2a	Pegasys	October 16, 2002	Birth defects and/or death of the fetus in combination with ribavirin	0.1
	Peginterferon alfa-2b	Pegintron	January 19, 2001	Birth defects and/or death of the fetus in combination with ribavirin	0.5
Others/Various	Danaparoid sodium	Orgaran	December 24, 1996	Spinal/epidural hematomas	1.1
Receptors	Etanercept	Enbrel	November 2, 1998	Risk of infections	9.4

Table 5. Risks for a First Safety-Related Regulatory Action

	No. of Biologicals	No. of Events	Follow-up, mo	Incidence Rate/1000 mo	HR (95% CI)
No small molecules previously approved in class ^a					
First biological	8	5	416.3	12.0	3.7 (1.5-9.5)
Later biologicals	162	35	11 916.8	2.9	1 [Reference]
Small molecules previously approved in class ^a					
First biological	19	9	1380.6	6.5	2.3 (1.1-4.8)
Later biologicals	151	31	10 952.5	2.8	1 [Reference]
Timing of approval					
January 1995-June 2001	90	23	9007.3	2.6	1 [Reference]
July 2001-June 2007	84	18	3737.4	4.8	1.5 (0.8-2.8)
Mechanistic classes					
Hormones	56	3	4885.2	0.6	1 [Reference]
Antibodies	44	19	2401.7	7.9	12.1 (3.6-40.9)
Cytokines	4	3	255.3	11.8	17.3 (3.5-86.1)
Enzymes	43	6	3247.0	1.8	2.9 (0.7-11.4)
Growth factors	6	2	344.7	5.8	8.2 (1.4-49.1)
Interferons	11	4	884.0	4.5	7.3 (1.6-32.8)
Receptors	3	2	69.0	29.0	34.2 (5.6-211.1)
Others/Various	7	2	579.4	3.5	4.9 (0.8-29.6)
Monoclonal antibodies					
Humanized	15	11	482.4	22.8	1 [Reference]
Chimeric	4	4	62.5	64.0	2.9 (0.9-9.9)
Murine	8	2	827.2	2.4	0.2 (0.03-0.7)

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aNot all biologicals could be classified according to position in class, and these biologicals were therefore excluded from the analysis.

Tumor necrosis factor, for example, is released by activated macrophages, T lymphocytes, and other immune cells and plays an important role in the human immune response to infections.^{27,28} As shown by the present study, the risk of infections with the tu-

mor necrosis factor antibody infliximab was identified and communicated after approval of the drug. The association between nonsteroidal anti-inflammatory drugs and the occurrence of gastrointestinal tract adverse events, however, illustrates that the

need for an in-depth evaluation of the mode of action counts also for small molecules.²⁹

There are limited data available in the literature on the timing and frequency of safety-related regulatory actions issued postapproval. The present study showed that the 174 biologicals had a probability of 14% to require their first safety-related regulatory action within 3 years after receiving marketing authorization, and the probability increased to 29% within 10 years after approval. In this context, it is important to notice that not all drugs are marketed immediately after approval and some drugs will never be marketed. Because all biologicals that obtained market authorization were included in the present study, this may have led to an underestimation of the probability of a safety-related regulatory action, which is a limitation of this study. Unfortunately, marketing status could not be retrieved from the US Food and Drug Administration and the EMEA Web sites.

Lasser et al²³ found that new chemical entities approved until 1999 had a probability of a black box warning of 10% after 10 years of marketing compared with 17% found in our study. Biologicals, therefore, seem to be more susceptible to a black box warning issued postapproval compared with new chemical entities in general. However, existing differences between both studies, with the inclusion of multiple black box warnings issued for the same drug and a delay in the occurrence of a black box warning in the *Physicians' Desk Reference* by Lasser et al,^{23,30} and an increasing awareness of patient safety and accessibility of safety data over time,³¹ preclude a direct comparison of probabilities.

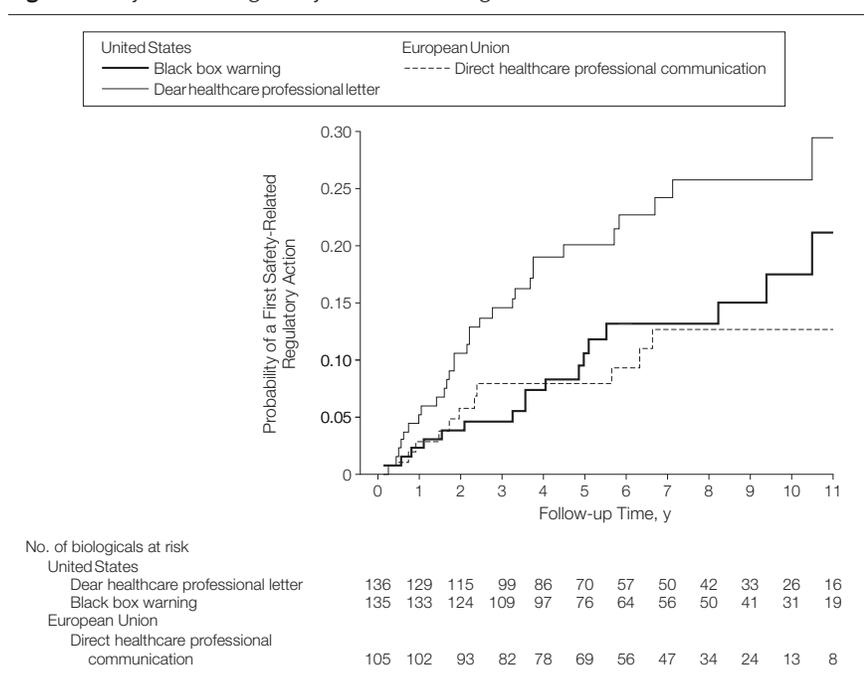
A limitation that should be addressed is the relatively small sample size and the small number of safety-related regulatory actions resulting in broad 95% CIs, which makes interpretation of nonstatistically significant findings challenging. However, it was decided to only include biologicals from 1995 onward because centralized decision making by the EMEA for all biologicals started in 1995.

Table 6. Safety-Related Regulatory Actions Classified at System Organ Class Level^a

System Organ Class Level	No. (%) of Safety-Related Regulatory Actions
Dear healthcare professional letter (United States)	
General disorders and administration site conditions	11 (16.2)
Infections and infestations	7 (10.3)
Blood and lymphatic system disorders	6 (8.8)
Immune system disorders	6 (8.8)
Others	38 (55.9)
Direct healthcare professional communication (European Union)	
General disorders and administration site conditions	6 (21.4)
Infections and infestations	6 (21.4)
Blood and lymphatic system disorders	3 (10.7)
Others	13 (46.4)
Black box warning (United States)	
General disorders and administration site conditions	5 (14.7)
Infections and infestations	5 (14.7)
Immune system disorders	5 (14.7)
Neoplasms benign, malignant, and unspecified	5 (14.7)
Others	14 (41.2)

^aMultiple primary safety warnings issued at the same time were included as multiple events.

Figure. Safety-Related Regulatory Actions for Biologicals



As shown in this study, the decision for a safety-related regulatory action can be based on (large) clinical trials, case reports, and/or epidemiological studies and thus also may be based on clinical observations without any formal epidemiological or experimental confirmation. In addition, the number of patients exposed to the different drugs may vary greatly, which may affect both detection of the safety problem as well as its significance for clinical practice. This dilemma in decision making—availability of incomplete data and variability in patient exposure—is acknowledged. However, dissemination of a safety-related regulatory action is usually the result of a balanced assessment by the regulatory authorities taking into account the seriousness of the safety problem and the need to inform health care professionals. Large epidemiological studies and/or clinical trials are often needed to confirm the association between the safety problem resulting in a regulatory action and the drug. The effect of epidemiological studies for the identification of safety problems could not be taken into account in this study because it was not possible to differentiate between safety problems identified by spontaneous reports and results from epidemiological studies based on the communications to health care professionals.

Some of the biologicals (for example, monoclonal antibodies) differ essentially from naturally occurring substances and might therefore be especially susceptible to adverse drug reactions.²⁶ Although the 95% CIs were broad, our study confirmed that these and other biologicals, including cytokines, growth factors, interferons, and receptors were specifically prone to safety-related regulatory actions. Within the group of monoclonal antibodies, the murine antibodies had a lower risk for a first safety-related regulatory action compared with the humanized monoclonal antibodies. However, this finding should be interpreted with caution due to the small number of monoclonal antibodies and safety-related regulatory actions.

The first biologicals approved in a chemical, pharmacological, and therapeutic subgroup were at a higher risk for their first safety-related regulatory action. This finding suggests that pharmacovigilance should especially be stringent for the first biologicals to be approved in a chemical, pharmacological, and therapeutic subgroup. Our study also showed that biologicals approved during the last 6 years of the study period (July 2001 to June 2007) had a non-significant higher risk for their first safety-related regulatory action compared with biologicals approved during the first 6.5 years of the study period (January 1995-June 2001). This higher risk is mainly due to the high number of DHPLs issued in 2005. Most of the biologicals approved in a new chemical, pharmacological, and therapeutic subgroup were approved during the first 6.5 years of the study period, which does not explain the higher risk for the first safety-related regulatory action for biologicals approved during the last 6 years of the study period.

Differences exist in the nature of the safety-related regulatory actions for biologicals compared with small molecules. As known from previous studies, most of the safety-related problems identified postapproval for the small molecules are identified in the system organ classes of hepatobiliary disorders, blood and lymphatic system disorders, cardiac disorders, and nervous system disorders.^{23,24,32} Knowledge on the nature of the safety events and the difference between the small molecules and the relatively new biologicals seems relevant. Lack of awareness of the nature of the safety issues related to the biologicals might hamper the link with the biological and its adverse event when a patient presents with a clinical problem.

More letters were disseminated in the United States compared with the European Union, which is in line with a previous observation that the approach to safety information appeared to be more conservative in the EU summary of product characteristics compared with the US package insert.³³ In

both regions, the dissemination of a letter can be initiated by the marketing authorization holder and by the authorities when important safety information has been identified and when important changes have been made to the product labeling.^{34,35} In addition, in the United States a letter can be issued to emphasize corrections to a prescription drug advertisement or to labeling as well.

Only 67 biologicals were approved in both regions within the study period. It should be noticed that some biologicals may have been approved in the other region prior to the study period. Of the 56 safety-related regulatory actions issued for these 67 biologicals, only 9 safety-related regulatory actions involved the same type of safety warning. This seems relevant because the other 35 and 8 safety-related regulatory actions issued in the United States and the European Union, respectively, were not issued in the other region. Because only the most recently approved summary of product characteristics were available from the EMEA Web site, it was not possible to investigate if adverse drug reactions communicated by a DHPL in the United States were already included in the EU summary of product characteristics or were added to the EU summary of product characteristics without communication by a DHPC. Six of the 9 warnings issued in both regions were issued within a period of 2 months.

In summary, this study has shown that almost 50% of the safety-related regulatory actions for biologicals were issued in the system organ classes of general disorders and administration site conditions, and infections and infestations. Warnings issued in the system organ class of infections and infestations were often related to the immunomodulatory effect of many biologicals. Although the limitations of preclinical trials for biologicals are acknowledged, results from pharmacology studies, preclinical studies, and clinical studies might result in the prediction of potential risks related to the drug for which close monitoring is needed in the postapproval setting. Health care pro-

professionals should be aware of the specific risks related to the relatively new class of biologicals to be able to provide a link between the use of the biological and the patient presenting with a clinical problem. In addition, the classes of antibodies (monoclonal), cytokines, growth factors, interferons, and receptors and the first biologicals approved in a chemical, pharmacological, and therapeutic subgroup are specifically prone to a first safety-related regulatory action; close monitoring of these biologicals is therefore recommended.

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Study concept and design: Giezen, Mantel-Teeuwisse, Straus, Leufkens, Egberts.

Acquisition of data: Giezen, Mantel-Teeuwisse.

Analysis and interpretation of data: Giezen, Mantel-Teeuwisse, Schellekens, Egberts.

Drafting of the manuscript: Giezen, Mantel-Teeuwisse.

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Administrative, technical, or material support: Giezen, Mantel-Teeuwisse, Egberts.

Study supervision: Mantel-Teeuwisse, Straus, Schellekens, Leufkens, Egberts.

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