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Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union Since 1995

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Conflict of interest

The department employing Drs Giezen, Mantel-Teeuwisse, Leufkens, and Egberts has received unrestricted research grants from GlaxoSmithKline, Organon, Merck, and NovoNordisk for the conduct of pharmacoepidemiological research.

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Introduction



Biologicals

- 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
- Biologicals have specific characteristics and therefore carry specific risks:
 - Complex production and purification process
 - High potential for immunogenicity
 - Limited predictability pre-clinical to clinical data
 - Toxicity often attributed to exaggerated pharmacology



Safety of drugs in the postmarketing setting

- Knowledge of new drugs is incomplete at time of approval, especially with reference to its safety profile
- Previous studies have shown that use of drugs in the postmarketing setting can lead to the identification of serious safety problems
- There is limited information available on the nature and timing of safety-related regulatory actions for biologicals



Key Message of the Study

Of 174 of these biologicals that were approved in the United States, the European Union, or both between January 1995 and June 2007:

- 82 safety-related regulatory actions were issued for 41 of these 174 biologicals (23.6%)
- Mean time to elicit a safety-related regulatory action was 3.7 years after approval
- Suggests need for more indepth evaluation prior to approval and highlights the importance of vigilance in post-marketing surveillance





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Methods



Objective of the Study

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



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Design and Setting

- Follow up of a group of biologicals approved in the United States and/or the European Union between January 1995 and June 2007
- In mechanistic classes: antibodies, cytokines, enzymes, growth factors, hormones, interferons, receptors, and others/various
- Exclusion of: biologicals with an extension of indication during the study period, vaccines, allergenic products, biological products for transfusion purposes



Main Outcome measures

- Safety-related regulatory actions between January 1995 and June 2008:
 1. Written communications to healthcare professionals;
 1. Dear Healthcare Professional Letters [DHPLs] in the United States and
 2. Direct Healthcare Professional Communications [DHPCs] in the European Union
 2. Postapproval “black box” warnings in the United States (indicating serious health hazard)
 3. Market withdrawals due to safety reasons in both the United States and the European Union



Source and Nature of the Safety Information

- Source of safety information in communications to health care professionals classified as
 - Postapproval reports (including spontaneous reports and pharmacoepidemiological studies and registries)
 - Clinical trial data
 - Combination of postapproval reports and clinical trial data
- Nature of safety information coded according to Medical Dictionary for Regulatory Authorities (version 9.1) at the System Organ Class level. Primary reason for dissemination of regulatory action included



Data analysis

- Study was analyzed comparable to a cohort of patients. However, in our study we followed a group of biologicals to determine
 - If first biologicals approved in (new) chemical, pharmacological, therapeutic subgroup have a higher risk compared to later representatives
 - If experience with biologicals (those approved at a later point in time) influences the number of safety-related regulatory actions
 - If the mechanistic classes, antibodies, cytokines, enzymes, growth factors, interferons, receptors, and various/others have a higher risk compared to hormones





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Results



Biologicals included

- 174 biologicals obtained approval between January 1995 and June 2007
 - 136 biologicals approved in the United States
 - 105 biologicals approved in the European Union
 - 67 approved in both regions



Safety-related regulatory actions

- Between January 1995 and June 2008, 82 safety-related regulatory actions were issued for 41 of 174 biologicals (23.6%):
 - 46 dear healthcare professional letters in the United States for 30 different biologicals
 - 17 direct healthcare professional communications in the European Union for 11 different biologicals
 - 19 “black box” warnings in the United States for 17 different biologicals
 - No marketing withdrawals related to safety



Timing and probability of safety-related regulatory action

- Mean time to elicit safety-related regulatory action was 3.7 years after approval
- 70.7% of safety-related regulatory actions issued within 5 years after approval
- Probability of a biological requiring its first safety-related regulatory action was (for the 174 biologicals):
 - 14% 3 years after approval
 - 29% 10 years after approval



Timing of approval and safety-related regulatory action

- Biologicals first to be approved in chemical, pharmacological, therapeutic subgroup had a nearly fourfold (HR, 3.7; 95% CI 1.5-9.5) higher risk for a first safety-related regulatory action compared to later representatives
- Biologicals approved between July 2001 and June 2007 had a non-significant higher risk (nearly 1 ½ times higher) for first safety-related regulatory action compared to biologicals approved between January 1995 and June 2001 (HR, 1.5; 95% CI, 0.8-2.8)



Comparison mechanistic classes of biologicals

Mechanistic class	Hazard ratio	95% Confidence Interval
Hormones	1 [Reference]	
Antibodies	12.1	3.6-40.9
Cytokines	17.3	3.5-86.1
Enzymes	2.9	0.7-11.4
Growth factors	8.2	1.4-49.1
Interferons	7.3	1.6-32.8
Receptors	34.2	5.6-211.1
Others/ various	4.9	0.8-29.6



Nature of safety information

- Nature of safety information mostly concerned classes
 - General disorders and administration site conditions
 - “Infections and infestations”
 - Immune system disorders



Source of safety information

- Dear healthcare professional letters in the United States:
 - 18 (39.1%) postapproval reports
 - 16 (34.8%) clinical trial data
 - 9 (19.6%) combination of postapproval reports and clinical trial data
 - 2 (4.3%) others
 - 1 (2.2%) unknown

- Direct healthcare professional communications in the European Union:
 - 9 (52.9%) postapproval reports
 - 5 (29.4%) clinical trial data
 - 1 (5.9%) combination of postapproval reports and clinical trial data
 - 1 (5.9%) others
 - 1 (5.9%) unknown





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Conclusions



Conclusions

- Nearly 1 in 4 biologicals that were approved between 1995 and June 2007 in the US and the EU had safety related regulatory actions taken, with the average time to regulatory action of 3.7 years
- Nature of safety-related regulatory actions mostly concerned the mode of administration or “infections and infestations”, related to the immunomodulatory effect of many biologicals
- More in-depth evaluation of the mode of action in (pre-)clinical studies might have resulted in better prediction of potential risks for which close monitoring is required, which is therefore recommended



Conclusions

- Healthcare professionals should be aware of specific risks related to this relatively new class to be able to provide a link between use of a biological and patient presenting with a clinical problem
- Close monitoring in postmarketing setting is recommended for all biological agents, especially for the first biological to be approved in a chemical, pharmacological, therapeutic class or subgroup

