

Monoclonal antibodies

Longitudinal prescribing information analysis of hypersensitivity reactions

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Abbreviations: mAbs, monoclonal antibodies; HSRs, hypersensitivity reactions; PI, prescribing information; IgE, immunoglobulin E; FDA, food and drug administration; MedDRA, medical dictionary for regulatory activities v14.0; NCI, national cancer institute; ADR, adverse drug reaction

Monoclonal antibodies (mAbs) are known to cause hypersensitivity reactions (HSRs). The reactions pose a significant challenge to investigators, regulators and health providers. Because HSRs cannot be predicted through the pharmacological basis of a therapy, clinical data are often relied upon to detect the reactions. Unfortunately, clinical studies are often unable to adequately characterize HSRs especially in therapies for orphan diseases. HSRs can go undetected until post-marketing safety surveillance when a large number of patients have been exposed to the therapy. The presented data demonstrates how hypersensitivity reaction warnings have changed over time in the prescribing information (PI), i.e., the drug package insert, through August 1, 2011 for 28 US-marketed mAbs. Tracking all PI revisions for each mAb over time revealed that hypersensitivity warning statements were expanded to include more severe manifestations. Over the course of a mAb therapy's life cycle, the hypersensitivity warning is twice more likely to be upgraded than downgraded in priority. Approximately 85% of hypersensitivity-associated fatality warnings were added in PI revisions as a result of post-marketing experience. Over 60% (20/33) of revisions to hypersensitivity warnings occurred within 3–4 y of product approval. While HSRs are generally recognized and described in the initial PI of mAbs, fatal HSRs are most commonly observed in post-marketing surveillance. Results of this study suggest that initial product labeling information may not describe rare but clinically significant occurrences of severe or fatal HSRs, but subsequent label revisions include rare events observed during post-marketed product use.

Introduction

Monoclonal antibodies (mAbs) are known to cause hypersensitivity reactions (HSRs); however, much is still unclear about the pathogenic mechanism of these rare but significant reactions.¹ HSRs can quickly escalate and lead to fatality. The reactions pose a substantial challenge to drug developers and clinical practitioners. Because HSRs cannot be predicted through the pharmacological basis of a therapy, clinical data are often relied upon to detect these rare reactions, but clinical studies done prior to approval often involve too few patients to adequately characterize HSRs, especially in therapies for orphan diseases. HSRs can go undetected until post-marketing safety surveillance, when a large number of patients have been exposed to the therapy.² The aim of this study was to determine whether revisions to prescribing information from approved mAbs support the need for additional vigilance to detect HSRs during post-approval use. Furthermore, our goal was to determine whether practitioners

and drug developers should expect to detect the reactions even if drug labeling may not have indicated that reactions were observed in clinical studies.

As protein therapeutics, mAbs are potentially immunogenic, i.e., they can be readily detected by the immune system as foreign.³ Because most approved mAbs are relatively large proteins (~150 kDa), they do not require haptentation and can rapidly cause a severe HSR or even fatal anaphylaxis. HSRs are commonly believed to be associated with immunoglobulin E (IgE)-mediated release of histamine, leukotriene, tryptase, prostaglandin from basophils and mast cells.³ IgE sensitization to a mAb after the initial exposure to the therapy is associated with HSRs in subsequent administrations. However, first-dose hypersensitivity/infusion reactions have also been observed. Immunoglobulin G and cytokine release syndrome mechanisms have been proposed as probable causes of first-dose hypersensitivity/infusion reactions.³

The poor predictability of HSRs in patients has become a substantial challenge for development of therapeutic

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Table 1. Monoclonal antibodies currently marketed in the United States (as of August 1, 2011)

Trade name	International non-proprietary name	mAb Type*	Year of first FDA approval
Orthoclone OKT3 [†]	muromonab-CD3	Murine	1986
ReoPro [®]	abciximab	Chimeric	1994
Rituxan [®]	rituximab	Chimeric	1997
Simulect [®]	basiliximab	Chimeric	1998
Synagis [®]	palivizumab	Humanized	1998
Remicade [®]	infliximab	Chimeric	1998
Herceptin [®]	trastuzumab	Humanized	1998
Campath [®] -1H	alemtuzumab	Humanized	2001
Zevalin [®]	Y90/In111-ibritumomab tiuxetan	Murine, radiolabeled	2002
Humira [®]	adalimumab	Human	2002
Xolair [®]	omalizumab	Humanized	2003
Bexxar [®]	I131-tositumomab	Murine, radiolabeled	2003
Tysabri [®]	natalizumab	Humanized	2004
Avastin [®]	bevacizumab	Humanized	2004
Erbitux [®]	cetuximab	Chimeric	2004
Lucentis [™]	ranibizumab	Humanized	2006
Vectibix [™]	panitumumab	Human	2006
Soliris [®]	eculizumab	Humanized	2007
Cimzia [®]	certolizumab pegol	Humanized	2008
Simponi [™]	golimumab	Human	2009
Ilaris [®]	canakinumab	Human	2009
Stelara [™]	ustekinumab	Human	2009
Arzerra [™]	ofatumumab	Human	2009
Actemra [®]	tocilizumab	Humanized	2010
Prolia [™] /Xgeva [™]	denosumab	Human	2010
Benlysta [®]	belimumab	Human	2011
Yervoy [™]	ipilimumab	Human	2011

*Distinction between a murine, chimeric, humanized and fully human antibody is in the human content of each type: murine (0%); chimeric (≥66%), humanized (≥90%) and human (100%).⁶ [†]Orthoclone OKT3 was delisted in May 2011 after the start of the study but is included in this analysis.

antibodies. Geographic variability in sensitizations has recently been described to be a further complicating factor in accurately characterizing the incidence and severity of HSRs in mAbs.⁴ A recent study suggested that HSRs to cetuximab, an anti-epidermal growth factor receptor mAb, have 2 fold greater incidence in North Carolina and Tennessee compared with New York.⁴ Regional environmental exposures have been attributed to the significant variability in HSR rates.⁴ The regional variability was not recognized in clinical trials and post-marketing experience revealed significantly higher incidence of HSRs in specific geographic areas in comparison to the incidence rate described in earlier versions of the prescribing information (PI), i.e., the drug package insert.

The PI is required by the US Food and Drug Administration (FDA) to accompany all prescription drug packages. The PI serves as a vital source of information of appropriate use and safety information to healthcare providers.⁵ Class analysis of the progression of mAb PIs provides direct insight into the hypersensitivity warning statements that prescribers consider when making therapeutic decisions.

Results

Analysis of 218 current and legacy PIs for 28 currently US-marketed mAbs (Table 1) was performed. Most current and previously-issued mAb PI revisions were obtained for the study, but some revised legacy PIs for Orthoclone OKT3[®] and ReoPro[®] were unavailable. Orthoclone OKT3[®] was delisted in May 2011 but was included because delisting occurred after the study was initiated. As expected, mAbs approved earlier in time had a greater number of PI revisions than more recently approved therapies.

The first part of the analysis included quantifying the number of mAb therapies that contained HSR warnings in their accompanying PI and when the warnings were first included in the PI. HSRs were described in 57% (16/28) of initial mAb PIs at the first availability of the therapy, while 75% (21/28) of the most current mAb PIs warned about the possibility of an HSR. Thus, 18% (5/28) of mAb therapies had an HSR warning statement added after the initial FDA-approval of the treatment. Of the therapies that had PIs revised to include HSR warnings in post-marketing, 80% (4/5) were approved prior to 1999.

In addition to newly added HSR warnings, each PI label revision was analyzed for changes to the description of the severity or frequency of HSRs if described in earlier PI versions. Twenty of 33 (61%) of the cumulative PI revisions for all mAbs with HSR warnings occurred within four years of product approval. The greatest number of revisions ($n = 9$) to the HSR warning statement were recorded during year four following product approval.

Each specific hypersensitivity-associated adverse event included in the PI was recorded and all revisions between PI versions were tracked. The five most common hypersensitivity-associated adverse events listed in mAb PIs included urticaria, bronchospasm, anaphylaxis, angioedema and hypotension. Manifestations of HSRs were commonly added to, removed from and moved to other sections of the PI. The ten most common manifestations were added to the PI or upgraded to a higher priority section more frequently than they were removed from the PI or downgraded to a lower priority section ($n = 58$ vs. $n = 14$).

In the PI, fatal HSR warnings appeared most frequently in subsequent label revisions after product launch. Fatal HSR warnings were described in 7% (2/28) of mAbs' initial PI. In the most current PI versions, 39% (11/28) of mAbs contained a fatal HSR warning. Thus, 82% (9/11) of mAbs that would eventually have a fatal hypersensitivity warning in the PI did not have one at the time of approval. Of the mAb PIs that were revised post-marketing to include fatal hypersensitivity warnings, the average elapsed time between approval and the time when the PI was revised to include fatal HSR ranged from 1.3 to 12.8 y with a mean of 4.4 y. With respect to antibody origin, mAb PIs that contained a fatal HSR warning included 100% (3/3) of murine, 60% (3/5) of chimeric, 30% (3/10) of humanized and 0% (0/9) of human. Seventy percent (7/10) of oncology mAbs contained a fatal HSR warning. Oncology mAbs accounted for 64% (7/11) of all mAbs that had a fatal HSR risk described in the PI. MAb administered via intravenous infusion and intravenous bolus accounted for 91% (10/11) of mAbs with a fatal HSR warning. No mAbs administered via the subcutaneous route had fatal HSR warnings.

Not all fatal mAb HSRs warnings were described in a boxed warning. Twenty-one percent (6/28) of mAbs had at least one PI version with an HSR boxed warning. Of the six mAbs, three PIs were revised to remove the HSR warning from the boxed warning. However, warnings of infusion reactions of uncertain origin were maintained in the boxed warning for each of the three mAbs.

Utilizing the PI Scoring Metric, HSR warnings were downgraded in significance in at least one version of a PI for 29% (8/28) of mAbs. However, HSR warnings were upgraded in significance in 83% (20/24) of mAbs that had at least one revision after initial PI. HSR warnings over time reflected HSRs occurring more frequently or deemed to be more severe than initially believed as depicted by the change in the section in which the warnings are described.

The scoring sum of the magnitude of upgrades to the severity in HSR warnings outnumbered downgrades (score = +165; score = -38) in the ten most commonly listed HSR manifestations (Fig. 1). Angioedema was the most frequently upgraded and

least frequently downgraded manifestation (score = +31). Scoring stratified by disease state categories for mAbs' indications did not produce any trends differing from the cumulative analysis of all mAbs.

The definitions and usage of key terms associated with HSRs in this study were recorded and tracked. The Medical Dictionary for Regulatory Activities v14.0 (MedDRA), the dictionary utilized by the FDA, was used as the standard for comparison. Inconsistent use of terminology among mAb PIs and PI revisions for a single mAb was observed. Ambiguous use of terms "infusion-related reactions" and "hypersensitivity" was common. Several discrepancies are depicted to illustrate the type of inconsistencies observed in the study. In early versions of their PIs, two mAbs, had "hypersensitivity" described in the boxed warning and the warnings and precautions section, but in subsequent revisions "hypersensitivity" was removed or downgraded from the sections and, overall, deemphasized. The term "infusion reactions" was subsequently used in the PIs to describe manifestations such as bronchospasms, angioedema and hypotension—all signs of an HSR. The PI for another mAb listed "allergic reactions" as a subset of the hypersensitivity adverse event, although MedDRA ontology lists the terms as synonyms. Another PI for a different mAb describes one of the defining events of "infusion reactions" as anaphylactoid responses that occur either within the first day or at any time following administration. The definition expands beyond NCI's clear defining boundaries of minutes to hours following infusion. Other discrepancies between use of HSR terminology in PIs and definitions established by NCI, FDA and MedDRA were observed but not quantified.

Discussion

Although the first therapeutic mAb was approved in 1986, these products were not approved on a regular basis until 1997. The well-distributed distribution of approval dates of mAb therapies during the past 15 y is reflected in the varying number of PI revisions for each therapy. The number of PI revisions is positively correlated with a product's duration of market availability. Reliable data on the yearly number of doses administered for every mAb included in this study was unavailable and neither drug sales nor the number of doses sold appropriately provides an estimate of doses administered across all 28 mAb therapies. Thus, additions, deletions and revisions to the hypersensitivity warning statement were best analyzed utilizing a temporal approach of the time elapsed after product launch.

The analysis suggests that more recent mAb therapies are more likely to include an HSR warning than mAbs approved prior to 1999. This finding may be explained by overall increasing trend in reporting of adverse drug reactions (ADRs) by health care providers, including those involved in clinical trials. However, the improved ADR reporting does not explain the finding that over 40% of changes to the HSR warning statements occurred after four years of mAb therapy availability. HSRs that occur with the administration of mAb therapies require substantial post-marketing time to be adequately characterized. Over the course of post-marketing experience the mAb PIs are more likely to gain

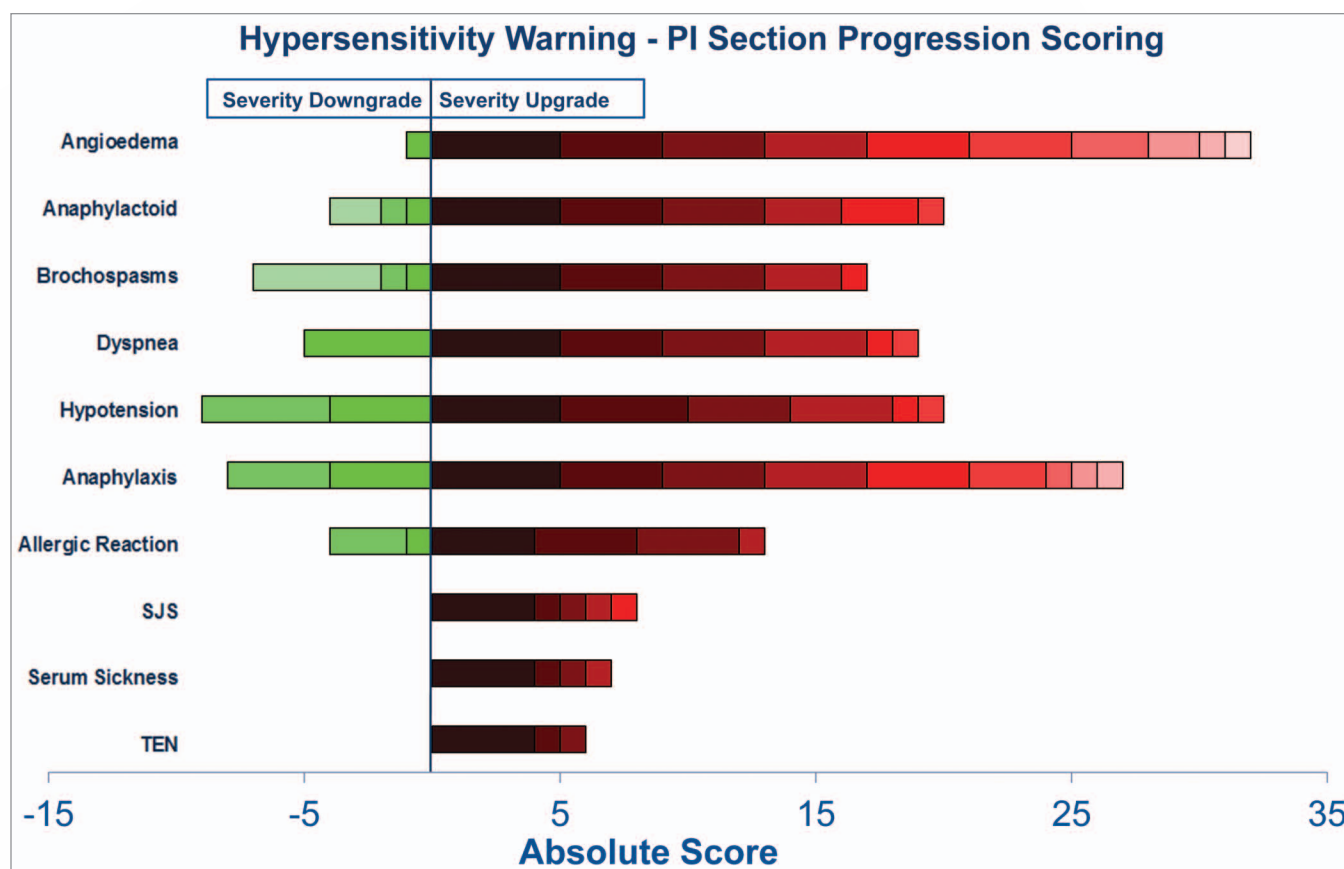


Figure 1. Scoring of the progression of the 10 most frequent manifestations of hypersensitivity between PI revisions. Progression is characterized by listing of manifestations in a different section than a prior version of a mAb's PI. Each increment is a single revision for any of the mAb PIs analyzed. An increment in a shade of red represents a single increase in score of a PI from a previous version. An increment in a shade of green represents a single reduction in score. Included is a summation of all revisions to PI versions of all mAbs from one PI version to the next.

additional detail and precaution regarding HSRs, which supports the point that HSR severity and frequency is underestimated at the time of therapy launch. While ADRs are commonly discovered in post-market surveillance, in the case of mAb HSRs, the first recognizable detection continues to occur after approval, even for those recently approved.

Fatal HSRs appear to be an even more challenging ADR to observe in clinical trials. The occurrence of fatal HSRs is poorly predicted by sponsors at the time of approval and health care providers should be aware of the risk even if not specified in the PI. Drug developers should also be cognizant of the possibility and should consider including a statement conveying that the mAb class of therapies is known for its risk of HSR reactions with rare incidence of fatalities in several products. The inclusion of the statement should be considered even if no previous severe HSR have been reported in clinical trials in order to improve preparedness of health care providers in the case of an occurrence.

The data set confirmed that murine content present in a mAb therapy is associated with an increased risk of HSRs. mAb therapies that include greater murine content more frequently had HSR warnings in their PIs. Furthermore, when stratifying the data by the therapies' primary indications, oncology mAbs had the greatest incidence of HSR warnings in their PIs. Practitioners

are more willing to bear the risk of HSRs for improved overall survival in potentially terminal diagnoses. Approved mAbs for inflammatory indications less frequently contain an HSR warning in their respective PIs compared with mAbs for oncology indications. A fatal HSR risk in an inflammatory disease state may be considered significant enough to outweigh the benefits in certain cases, a primary consideration in FDA's decision in approving a therapy. Therefore, mAb therapies with inflammatory or other non-terminal indications with HSR risk may be unable to prove enough benefit to outweigh its risks and gain FDA approval.

Terminology inconsistencies were prevalent across different mAbs and PI versions for a single mAb. Substantial discrepancies were found in the usage of terms "Hypersensitivity Reactions" and "Infusion Reactions" when comparing PIs of one therapy to another. The FDA defines a hypersensitivity reaction as "a local or general reaction of an organism following contact with a specific allergen to which it has been previously exposed and to which it has become sensitized,"⁷ and the National Cancer Institute (NCI) defines an infusion reaction as "a reaction to the infusion of pharmacological or biological substances" where "symptoms may appear within minutes to hours following the infusion..."⁸ The distinction between the definitions being that

infusion reactions is suggested to be an encompassing term that includes, but not necessarily equate to, hypersensitivity reactions. The justification and intent of the two mAbs with PIs that changed a “hypersensitivity” warning statement to an “infusion reaction” warning in a revised PI is unclear. However, the term “infusion reaction” may be interpreted as a less alarming adverse event to practitioners than “hypersensitivity.” Removal of HSR warnings from the boxed warning in favor of non-specific infusion reactions in PIs may demonstrate the sentiment of sponsors to prefer milder warning statements.

Other instances of improper usage of HSR-related terms in PIs may be attributed to unclear guidance in years prior to adoption of MedDRA as to which ontology and medical dictionary should be the standard for ADR reporting and detailing. The examples of inconsistencies all originated from therapies released prior to 2005 and the implementation of Structured Product Labeling by the FDA. Reporting of ADRs in clinical trials is done by health care providers in various countries with potentially varying interpretation of terms such as “hypersensitivity reactions” and “infusion-related reactions.” However, the usage of the terms in the PI is drafted by the drug developer and approved by the FDA. The discrepancies between various versions of single mAb’s PI and PI of different mAb therapies may be explained by the evolving terminologies used in describing allergic reactions. MedDRA has had 13 prior versions and NCI’s Common Terminology Criteria for Adverse Events (CTCAE) is on its fourth version. Improper use of medical terms can have an impact on the way health care providers interpret relative risk of therapies gathered from the PI.

Results from the study suggest that over the course of the mAb therapy’s life cycle HSRs are recognized to be more significant as represented by a greater number of upgrades than downgrades in priority. The greater priority of the HSR warnings was demonstrated by being included in PI sections of greater clinical significance over time. While the majority of mAbs’ initial PI contained a hypersensitivity warning, the number of listed manifestations associated with hypersensitivity increased with PI revisions. Fatal HSRs were most commonly detected after product approval during post-marketing surveillance and hypersensitivity-associated fatality warnings were added to the PI in subsequent revisions. Furthermore, regulatory agencies may consider the establishment of a class-wide statement for mAbs regarding the potential of HSRs and HSR-related fatalities, even in the absence of reports in clinical studies.

Substantial inconsistent use of terminology was common when comparing different PI versions and the commonly accepted definitions. The findings of inconsistent terminology use should make health care providers cautious of potential differences of how an HSR is described in one PI vs. another. Drug developers should continue to work toward standardization of terminology use in accordance to MedDRA, the dictionary utilized by the FDA in ADR reporting.

Materials and Methods

A qualitative and quantitative analysis was conducted on all available current and legacy PIs for all US marketed mAbs as

Table 2. PI section scoring metric

PI Section Scoring Metric (Highest Priority Warning)	
Score	Section
5 points	Boxed Warning
4 points	Warnings and Precautions
3 points	Adverse Reactions: listed as “most common”
2 points	Adverse Reactions: listed as “resulting in discontinuation”
1 points	Adverse Reactions: listed as “other reactions”
(Lowest Priority Warning)	

of August 1, 2011 (Table 1). Each PI version was tracked for changes, additions and deletions to the content of the safety information relating to an HSR warning. PI versions were obtained from several sources including *Drugs@FDA*, *DailyMed*, *Physicians’ Desk Reference*, *PharmaPendium (Elsevier)*, drug sponsors’ websites and archives of various healthcare-related websites of reliable origin.

Terms including “hypersensitivity,” “allergic reactions,” “anaphylaxis” and “anaphylactoid” were tracked and recorded reflecting the risk of an HSR. Additionally, the term “infusion-related reactions” and its synonyms were considered equivalent to an HSR if the term was described in the same context as at least one “Allergic Conditions” lower level term from Medical Dictionary for Regulatory Activities v14.0 (MedDRA). Analysis was based on a temporal relationship between revisions to mAb PIs with respect to hypersensitivity since comprehensive dose utilization data for each therapy is unavailable. Between PI revisions, hypersensitivity and all accompanying manifestations were recorded and analyzed for additions and deletions, as well as changes in the relative significance of the warning.

To assess the relative significance of an HSR warning, sections within the PI in which HSR manifestations appeared were recorded and scored. A scoring metric was devised to track the changes in the sections HSR manifestations were described in the PI versions (Table 2). The PI section scoring metric was based on FDA’s “Guidance for Industry” documents on labeling.^{9,10} HSRs listed in PI sections of greater safety priority received a higher score. Relative changes in the score between PI revisions were analyzed for individual manifestation of hypersensitivity. A single manifestation listed in multiple sections received a single score for the highest priority section. Warnings in the “Adverse Reactions” section described as “resulting in discontinuation” often were also listed in other sections of higher priority and received the greater score of the two. To illustrate the application of the scoring metric, a PI with a particular hypersensitivity manifestation that was moved from being listed in “Adverse Reactions: listed as ‘most common’” to the “Boxed Warning” had its warning upgraded in significance by +2 points (5-3). An HSR warning that was initially listed in “Warnings and Precautions” section and then removed from the PI altogether had its warning downgraded in significance by -4 points (0–4). Newly listed HSR manifestations not included in previous versions of the PI were considered upgrades in significance and received a positive score.

The study also recorded instances in the PI where definitions and defining manifestations of the key terms associated with

HSRs were described. At the start of the study, the definitions and usage of HSR-related terms were documented in order to support the established defining criteria for the study. As the study progressed, the key term usage and definitions were recorded in order to portray the common inconsistencies in the use of HSR terminology among drug developers.

Study limitations. The PI represents a select set of data that may not include information that may more accurately portray the incidence and severity of HSRs. The intent of the study was to follow the progression and evolution of HSR warnings within the PI, which is heavily relied upon by health practitioners. Comparison of incidence or severity of HSR and how it evolved with post-marketing experience cannot be fully accomplished through PI progression analysis, but such data gathered provides insight into the trends of HSRs PI inclusion.

Results may be confounded by the rate of uptake by prescribers after approval of a therapy. The sooner a drug is administered to a large patient population, the greater the likelihood that rare adverse events will be detected earlier in a product's life cycle. Post-marketing safety reports guide revisions to the PI. Safety data are not readily available on all therapies included in this study and doses administered cannot be accurately derived from sales data.

In 2006, the FDA implemented guidelines to transition PIs to a standardized format. PIs that transitioned to the new format

may have excluded some safety information described in previous versions in order to comply with the new standards.

The PI metric score utilized to determine relative changes to the section in which HSR warnings were described may not depict the real significance of the movements from one section to another, and the scoring may not necessarily reflect health practitioners' views on the level of importance a warning listed in one section of the PI over another.

Additionally, not all legacy PI versions for Orthoclone OKT3® and ReoPro®, the first two mAbs approved by the FDA, were obtained.

Disclosure of Potential Conflicts of Interest

At the time of this research, Konstantin Kleyman was employed by MedImmune as a student intern. Debra S. Weintraub is employed by MedImmune and is a minority owner of company stock (AstraZeneca). The authors declare no further relationships/conditions/circumstances that present a potential conflict of interest.

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