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Selective Safety Data Collection in Clinical Studies of Oncology Drugs for Marketing Approval in the United States

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Abstract

Optimization of data collection is a key issue in clinical studies of oncology drugs because it affects the workload and financial burden of the clinical infrastructure. Focusing on oncology drugs, which produce many low-grade as well as serious adverse reactions, we investigated the use of selective safety data collection in the pivotal clinical studies for marketing approval in the United States.

Drug labels were examined to find clinical studies that evaluated adverse events with limited data, and found ten drugs approved between 2004 and 2015 whose pivotal studies used selective rather than comprehensive safety data collection. Only three were in accordance with the 2001 FDA Guidance for Industry, "Cancer Drug and Biological Products – Clinical Data in Marketing Applications", which suggests such selectivity when targeting a similar population to the initial approval. Two selective studies were applied to a drug's initial approval. Three adopted the guidance criteria for safety data collection of only noting grade 4-5 hematologic and 3-5 non-hematologic toxicities.

No major problems caused by this approach were found in the description of medical reviews, approval letters and post-marketing revisions to the boxed warnings on labels issued by the FDA. Selective safety data collection can be an efficient approach to streamlining the procedure of clinical studies and should be considered for use in pivotal clinical studies for oncology drugs.

Keywords: oncology drug, safety data collection, Food and Drug Administration, guidance for industry, clinical study, adverse event

1. Introduction

Data from clinical studies are necessary for the marketing approval of drugs. Usually, all adverse reactions observed in all patients enrolled in the clinical studies are collected and evaluated in both the first approval and supplemental approval processes for every new indication of the relevant drug. In clinical studies of oncology drugs, the frequency and severity of adverse reactions are greater than those of drugs targeting other diseases. Therefore, the management of safety data sometimes causes a substantial workload and financial burden in clinical studies [15, 13, 19].

The Council for International Organizations of Medical Science (CIOMS) Working Group VI noted that an all-inclusive approach for safety data collection in clinical studies places an undue burden on the investigator and sponsor and diverts attention from more important matters (see Section IV, entitled "Collection and management of safety data during clinical trials") [4]. As an efficient approach to collecting safety data, the Working Group VI recommended that once the safety profile of a marketed product is judged to be well understood and established, it may be acceptable to collect less data. While detailed information on serious adverse events should always be collected, for well-established products it may be appropriate to collect non-serious adverse events only if suspected by the investigator to be related to the compound.

In 2001, FDA issued the Guidance for Industry, "Cancer Drug and Biological Products – Clinical Data in Marketing Applications" [24]. The purpose of this guidance was to provide recommendations for sponsors on data collection for cancer clinical trials submitted to FDA to support marketing claims in new drug applications (NDAs), biologics license applications (BLAs), or supplemental applications for new indications. In its general considerations, the guidance mentions that the agency recognizes that the collection, quality control, and entry of data in a database is an expensive and time-consuming process. As a recommendation for data collection of evidence of toxicity, it notes that in supplemental efficacy applications that propose a new use for an already marketed drug in a similar population, additional data on grade 1–2 non-hematologic toxicity and grade 1–3 hematologic toxicity may not be important and may not need to be collected.

Other investigators have reported issues with excessive data collection in clinical studies of oncology drugs. Mahoney *et*

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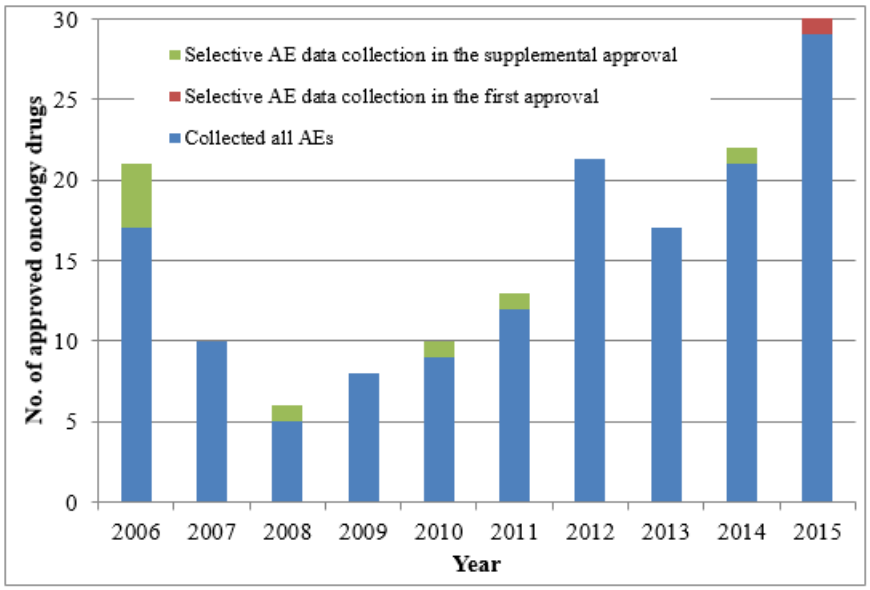

Figure 1: Approved oncology drugs by FDA by year.

al. surveyed adverse events reported from 26 clinical studies sponsored by The North Central Cancer Treatment Group (NCCTG) [8]. They found that only 3% of the routinely reported adverse events were ≥ grade 3, and they concluded that most events were not clinically important. O'Leary *et al.* evaluated 8 studies conducted by the Ontario Clinical Oncology Group [10]. They reported that the total collected data items per subject ranged from 186 to 1035 per trial with a median of 599. On the other hand, only a median of 96 data items (18%) were actually reported in each manuscript, ranging from 11% to 27% per trial. Kaiser *et al*. analyzed eight sets of safety data from randomized trials of oncology drugs [7, 1, 20, 21]. They proposed that in clinical studies for supplemental approval, grade 1–2 events need not be collected and grade 3 events should be collected in a subsample of the full trial, whereas serious events should be collected comprehensively.

Although the CIOMS report, FDA guidance and previous studies have stressed the potential of not collecting unnecessary data, no study such as ours, which focuses on selective safety data collection in clinical studies for new oncology drugs, has yet been presented to our knowledge. It could be important to learn how selective safety data collection is currently applied when discussing this approach.

In the present study, we investigated the use of selective safety data collection in the pivotal clinical studies for marketing approval of new oncology drugs over the last 10 years in the USA.

2. Material and Methods

2.1. Targeted Drugs and Data Source

Oncology drugs that received initial or supplemental approval for marketing by the FDA between 2006 and 2015 were evaluated. Labels, approval letters and medical reviews of oncology drugs were obtained from the pages of Drugs@FDA on the FDA website [23].

2.2. Investigation on Approvals with Selective Safety Data Collection

We examined the section of "adverse reactions" in the labels of oncology drugs and extracted pivotal studies that adopted selective safety data collection. The criteria for the safety data collection were assessed based on the description of the FDA guidance "Cancer Drug and Biological Products – Clinical Data in Marketing Applications" issued in 2001 [24]. Approval letters were used to investigate the post-marketing requirements [25, 28, 31, 33, 34, 35, 37, 26, 29]. Medical reviews issued by the Center for Drug Evaluation and Research (CDER) were used to investigate safety evaluation by U.S. authorities [25, 27, 30, 32, 39].

2.3. Post-Market Safety Issues

Post-market safety data issues after approval with selective safety collection were investigated by searching for amendments of the boxed warnings in the labels and changes to safety information for health care professionals from the pages of "Other Important Information from FDA" of each drug on Drugs@FDA on the FDA website [23].

3. Results

3.1. The Number of Approved Oncology Drugs with Selective Safety Data Collection

Figure 1 shows the number of oncology drugs that were approved by the FDA by year. There were 159 approvals of oncology drugs between 2006 and 2015. The number of approvals

Drug name Approval year	Initial or supplemental approval	Indication	Initial indication	Adverse event	Grade			
					1	2	3	4-5
FDA Guidance 2001				Hematologic				○
				Non-Hematologic			○	○
Dinutuximab 2015	Initial	Pediatric neuroblastoma	NA	Hematologic			○	○
				Non-Hematologic			○	○
Bevacizumab 2014	Supplemental	Ovary	Colorectal 1st line	Hematologic		○	○	○
				Non-Hematologic		○	○	○
Rituximab 2011	Supplemental	NHL maintenance	NHL	Hematologic			○	○
				Non-Hematologic		△	○	○
Rituximab 2010	Supplemental	CLL	NHL	Hematologic			○	○
				Non-Hematologic			○	○
Bevacizumab 2008	Supplemental	Breast	Colorectal 1st line	Hematologic				○
				Non-Hematologic			○	○
Trastuzumab 2006	Supplemental	Breast adjuvant	Breast metastatic	NSABP B-31 study				
				Hematologic		△	○	○
				Non-Hematologic		△	○	○
				NCCTG N9831 study				
				Hematologic			○	○
				Non-Hematologic	△	△	○	○
Bevacizumab 2006	Supplemental	NSCLC	Colorectal 1st line	Hematologic				○
				Non-Hematologic			○	○
Pagaspargase 2006	Supplemental	ALL 1st line	ALL refractory	CCG-1962				
				Hematologic	△	△	△	△
				Non-Hematologic	△	△	○	○
				Study 2				
				Hematologic				
				Non-Hematologic			○	○
Bevacizumab 2006	Supplemental	Colorectal 2nd line	Colorectal 1st line	Hematologic				○
				Non-Hematologic			○	○
Bevacizumab 2004	Initial	Colorectal 1st line	NA	Hematologic	△	△	○	○
				Non-Hematologic	△	△	○	○

○: Collected all events, △: Collected partly

Table 1: Approved oncology drugs using selective safety data collection.

has been gradually increasing since 2008. Among them, nine approvals included pivotal clinical studies that adopted selective safety data collection: one for the initial approval and eight for supplemental approval for additional indications.

3.2. Approvals with Selective Safety Data Collection

Table 1 shows the approved oncology drugs which adopted selective safety data collection in the pivotal studies. In addition to the nine cases approved between 2006 and 2015, the initial approval for bevacizumab in 2004 was investigated because its pivotal study also adopted selective safety data collection. All the drugs except pagaspargase were molecular-targeting, monoclonal antibodies. The 2001 FDA guidance states that "In supplemental efficacy applications that propose a new use for an already marketed drug in a similar population, additional data on grade 1-2 non-hematologic toxicity and grade 1-3 hematologic toxicity may not be important and may not need to be collected" [24]. Among the ten approvals shown in Table 1, three – pagaspargase (ALL), trastuzumab (breast cancer) and rituximab (NHL) – were targeted at a similar population as the initial approvals from the viewpoint of tumor type and usage. Four approvals – bevacizumab (NSCLC, ovary cancer and breast cancer) and rituximab (CLL) – were targeting different tumor types than their initial approval. One approval – bevacizumab (colorectal cancer as 2nd line therapy) – was for a different combination of the drug. Two – dinutuximab (pediatric glioblastoma) and bevacizumab (colorectal cancer for 1st line therapy) – were for the initial approvals.

The criteria for safety data collection in each pivotal study, as described on their labels, are shown in Table 2. Three approvals – bevacizumab (colorectal cancer for 2nd line therapy, NSCLC and breast cancer) – adopted the same criteria for data collection as stated in the 2001 FDA guidance; only grade 3–5 non-hematologic and grade 4–5 hematologic adverse events were collected. These three clinical studies were conducted by a non-commercial clinical study group (Eastern Cooperative Oncology Group, ECOG). Several other studies with selective safety data collection were sponsored by pharmaceutical companies. Two approvals – trastuzumab and pagaspargase – collected all grades of characteristic toxicities: cardiac toxicities for trastuzumab and asparaginase-induced adverse reactions for pegasparagase.

Drug name Approval year	Indication	Description on safety data collection on the label (Study name, No. of pts in study arm) Sponsor or funder
Dinutuximab 2015	Pediatric neuroblastoma	Adverse reactions of Grade 3 or greater severity were comprehensively collected, but adverse reactions of Grade 1 or 2 severity were collected sporadically and laboratory data were not comprehensively collected. (DIV-NB-301, 134) National Cancer Institute (*28*)
Bevacizumab 2014	Ovary	AEs grade 2–5 occurring during the study and up to 30 days after the last dose of study medication will need be recorded in the eCRF* (*29*). (AURELIA, 179) F. Hoffmann-La Roche (*30*)
Rituximab 2011	NHL	Detailed safety data collection was limited to serious adverse reactions, Grade ≥ 2 infections, and Grade ≥ 3 adverse reactions. (PRIMA, 505) F. Hoffmann-La Roche (*31*)
Rituximab 2010	CLL	Detailed safety data collection was limited to Grade 3 and 4 adverse reactions and serious adverse reactions. (REACH, 408) F. Hoffmann-La Roche (*32*)
Bevacizumab 2008	Breast	Only Grade 3−5 non-hematologic and Grade 4−5 hematologic adverse events were collected. (E2100, 363) ECOG (*33*)
Trastuzumab 2006	Breast adjuvant	Only Grade 3−5 adverse events, treatment-related Grade 2 events, and Grade 2−5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. (NSABP B-31, 1200) NSABP (*34*)
		Data collection was limited to the following investigator-attributed treatment-related 282 adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3−5 non-hematologic toxicities, selected Grade 2−5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, sensory neuropathy) and Grade 1−5 cardiac toxicities occurring during chemotherapy and/or Herceptin treatment. (NCCTG N9831, 1154) NCCTG (*34*)
Bevacizumab 2006	NSCLC	Only Grade 3-5 non-hematologic and Grade 4-5 hematologic adverse events were collected. (E4599, 427) ECOG (*35*)
Pagaspargase 2006	ALL	Detailed safety information was collected for pre-specified adverse reactions identified as asparaginase-induced adverse reactions and for grade 3 and 4 non-hematologic adverse reactions according to the Children's Cancer Group (CCG) Toxicity and Complication Criteria. (CCG-1962, 58) Children's Cancer Group and Rhone-Poulenc Rorer (*36*)
		Safety data were collected only for National Cancer Institute Common Toxicity Criteria (NCI CTC) version 2.0, grade 3 and 4 non-hematologic toxicities. (Study 2, not described) unknown
Bevacizumab 2006	Colorectal	Only Grade 3-5 non-hematologic and Grade 4−5 hematologic adverse events related to treatment were collected. (E3200, 287) ECOG (*37*)
Bevacizumab 2004	Colorectal	All Grade 3−4 adverse events and selected Grade 1−2 adverse events (hypertension, proteinuria, thromboembolic events) were collected in the entire study population. Grade 1−4 adverse events were collected for the first approximately 100 patients in each of the three treatment arms who were enrolled until enrollment in Arm 3 (5-FU/LV + Avastin) was discontinued. (AVF2109g, 392) Genentech (*38*)

*: Described in AURELIA study protocol

Table 2: Description on safety data collection on the label.

3.3. Medical Review by CDER and Post-Marketing Requirement in Approval Letter

We obtained five Medical or Summary Reviews issued by CDER for approvals using selective data collection as shown in Table 3. In the reviews of dinutuximab and bevacizumab for breast cancer, caution or limitations in the interpretation of toxicity data due to selective safety data collection were emphasized [32, 39]. In the reviews of bevacizumab for NSCLC, colorectal cancer as 2nd line and 1st line therapy, no major problems caused by selective safety data collection were described [25, 27, 30]. However, in the review of bevacizumab for colorectal cancer as a 2nd line therapy, other serious problems

Drug name Approval year	Indication	Description of safety data collection in medical review issued by CDER
Dinutuximab 2015	Pediatric glioblastoma	- Data regarding mild adverse events should be interpreted with caution because data for mild adverse events were not systematically and comprehensively captured. (*27*)
Bevacizumab 2008	Breast	- Limitations in toxicity data collection preclude an evaluation on mild or moderate toxicities as a signal for severe or life-threatening adverse drug reactions occurring at a low frequency and modestly increased above the background rate. (*26*)
Bevacizumab 2006	NSCLC	- The data collected in this study were limited, such that comparative toxicity could be evaluated only for severe and serious adverse events. Based on the review of the safety data, no new safety signals other than hyponatremia were identified. - Data regarding the incidence of, and reason for, Avastin dose modification were not collected nor were data regarding the toxicities leading to treatment discontinuation collected. (*25*)
Bevacizumab 2006	Colorectal 2nd line	- Events unlikely to be related to protocol therapy, but not able to be ruled out, were not reported. - The onset dates of adverse events were not collected. - Adverse events that led to the discontinuation or reduction in the dose of bevacizumab were not collected. (*24*)
Bevacizumab 2004	Colorectal 1st line	- During pre-Phase 3 meetings, the sponsor chose to collect grade 1-2 events in the first 211patients randomized to a bevacizumab containing arm. (*23*)

Table 3: Description of safety data collection in medical or summary review by CDER.

were pointed out, such as the fact that several important safety items were not reported. This issue resulted in the following caveat on the label: "These data are likely to underestimate the true adverse event rates due to the reporting mechanisms used in the Study" [27].

According to the FDA's medical reviews, the initial approval of dinutuximab in 2015 was based on the safety database of 1,184 patients in seven studies [39]. The initial approval of bevacizumab in 2004 was based on a safety database of 1,032 patients in eleven studies including not only colorectal but also breast, non-small cell lung and other solid tumors [25].

We examined approval letters for ten approvals and found no evidence of post-marketing requirements following approval based on studies with selective safety data collection.

3.4. Post-Market Safety Issues

Post-market safety issues were investigated for five oncology drugs approved on the basis of selective safety data: dinutuximab, bevacizumab, rituximab, trastuzumab, pegasparagarse. Among them, Hepatitis B virus (HBV) reactivation for rituximab and embryo-fetal toxicity in a pregnant woman for trastuzumab were added to the respective labels after the approvals, using selective safety data collection as shown in Table 4. Safety information on Microangiopathic Hemolytic Anemia (MAHA) for bevacizumab and Hepatitis B virus (HBV) reactivation for rituximab were issued for health care professionals after their approvals, as shown in Table 5.

4. Discussion

In the present study, we found that the number of oncology drugs approved based on studies using selective safety data collection was relatively small. This result suggests that selective safety data collection is not a common approach, even though the 2001 FDA guidance states that "In supplemental efficacy applications that propose a new use for an already marketed drug in a similar population, additional data on grade 1-2 nonhematologic toxicity and grade 1-3 hematologic toxicity may not be important and may not need to be collected" [24]. In 2012, the FDA issued the draft guidance, "Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post approval Clinical Investigations" and recommended adopting selective safety data collection in clinical studies [36]. However, there has been no evident trend of increasing use of selective safety data collection since the issue of the draft guidance.

The risk of rituximab reactivating HBV and the risk of embryo-fetal toxicity for trastuzumab were added to these drugs' labels after their initial approval on the basis of selective safety data collection. These populations, i.e., patients with HBV and pregnant women, are usually excluded from clinical studies for approval, so different measures than selective data collection should be taken for these patients. Safety information on Microangiopathic Hemolytic Anemia (MAHA) for bevacizumab in combination with sunitinib was also issued for

Drug	Boxed Warning as of the initial approval	Amendment
Dinutuximab	- Infusion reactions - Neuropathy	None
Bevacizumab	- Gastrointestinal perforations - Surgery and wound healing complications - Hemorrhage	None
Rituximab	- Fatal infusion reactions - Tumor Lysis Syndrome (TLS) - Severe mucocutaneous reactions	- Progressive multifocal leukoencephalopathy (PML), added in Feb. 2007. - Tumor Lysis Syndrome (TLS), deleted in Sep. 2013. ***- Hepatitis B virus (HBV) reactivation, added in Sep. 2013.***
Trastuzumab	Cardiomyopathy	- Hypersensitivity reaction including anaphylaxis, added in Dec. 2001. - Infusion reactions, added in Dec. 2001. - Pulmonary events, added in Dec. 2001. ***- Embryo-Fetal Toxicity, added in Oct. 2010.***
Pegaspargase	None	None

Note: Bold italic indicates the warning added after the approval with selective data collection

Table 4: Amendments to boxed warnings of labels.

Drug	Date	Subject
Dinutuximab		None
Bevacizumab	July 2008	***Microangiopathic Hemolytic Anemia (MAHA) in Patients treated with Avastin® (bevacizumab) and sunitinib malate***
Rituximab	Sep. 2013	***Boxed Warning and new recommendations to decrease risk of hepatitis B reactivation with the immune-suppressing and anti-cancer drugs Arzerra (ofatumumab) and Rituxan (rituximab)***
Rituximab	Dec. 2006	Public Health Advisory: Life-threatening Brain Infection in Patients with Systemic Lupus Erythematosus After Rituxan (Rituximab) Treatment
Trastuzumab		None
Pegaspargase		None

Note: Bold italic indicates the warning added after the approval with selective data collection

Table 5: Post-market drug safety information for health care professionals.

health care professionals. This combination therapy has not been approved yet. These results suggest that few serious safety issues caused by selective safety data collection are likely to happen in the post-market stage.

Only three out of the ten approvals we examined targeted a similar population to the initial approvals in accordance with the 2001 FDA guidance. Other approvals targeted a different tumor type or different usage, or were for initial approval. In the cases of initial approvals for dinutuximab and bevacizumab, over 1,000 patients were included in the safety database. From the results of the present study examining approval cases, it is likely that the safety profiles of relevant oncology drugs are considered to be well established by the safety data of applications for a different tumor type or usage in the initial ap-

proval or other prior-phase clinical studies. In 2016, the FDA issued a guidance "Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Post approval Clinical Investigations" [40]. This guidance was aimed at all human drugs and biological drug products regulated by CDER or CBER, including oncology drugs. It mentions that selective safety data collection may be appropriate in the following types of clinical investigations: (1) clinical investigations of new indications of approved drugs, (2) post-approval clinical studies and trials conducted to fulfill post-marketing requirements and post-marketing commitments, (3) late-stage premarket and post-approval outcome clinical trials, (4) premarket clinical investigations for some original applications, (5) post-approval clinical investigations in a different patient population or with different doses or other conditions of use. Among them, contingency (1) is the same category as that in the 2001 FDA guidance, namely, targeting a similar population to the initial approval. In the present study, contingency (4) was represented by the initial approval of dinutuximab and bevacizumab, and (5) was represented by bevacizumab (NSCLC, ovary, breast and colorectal cancer for 2nd line therapy) and rituximab (CLL). Selective safety data collection may be applicable to a wider range of pivotal studies than simply those targeting a similar population as the initial approval.

In three of the ten cases studied, safety data were collected based on the same criteria as the 2001 FDA guidance. All grade 3 and 4 events were collected in most cases and toxicities characteristic of the particular drugs in several cases in the present study. The 2016 FDA guidance states that in the oncology setting, data from all grade 3 and grade 4 adverse events, as well as grade 2 adverse events that affect vital organs (e.g., heart, liver), should always be collected [40]. This statement was not seen in the 2001 FDA guidance, but seems reasonable in terms of essential safety data collection.

Selective safety data collection was applied to clinical studies conducted by pharmaceutical companies as well as clinical study groups. In the latter type of studies, other issues were often pointed out in the evaluation for approval by FDA. It is important to clarify the necessary safety data for approval, especially for clinical study groups.

Both the 2001 and 2016 FDA guidances encouraged sponsors to discuss with FDA at meetings, such as end-of-phase-2 meetings for a phase 3 trial to specify the data appropriate for safety data collection [24, 40]. This is an important step to determine whether the plan for selective data collection is acceptable for drug approval.

As one limitation of the present study, we could not discern why selective data collection has not been widely used, despite this issue being introduced by the 2001 FDA guidance. It may be that selective safety data collection has been introduced on a case-by-case basis, and detailed conditions for adopting this approach have not been established [36]. The present authors previously reported the applicability of selective data collection based on tumor type and usage for supplemental approval [22]. Further investigation is needed on this issue.

We could not investigate pivotal studies that did not obtain drug approval by FDA. Therefore, we did not know the total number of pivotal studies that adopted selective safety data collection. As far as authors know, North Central Cancer Treatment Group (NCCTG) introduced the concept of comprehensive safety data collection for only the initial 300 patients of their phase 3 adjuvant trial (N0147) for colon cancer [8, 2]. Safety data for patients enrolled beyond the 300th patient (per arm) were collected only if of maximum severity, at the end of the study treatment. The NCCTG also developed the NCCTG Routine Adverse Event Data Submission Policy [8]. According to this policy, all adverse events pre-specified in the case report form were collected regardless of the grade or attribution. However, as for other adverse events, grade 2 events that are considered unlikely to be related to study drugs were not collected. We did not find any clinical studies that adopted this policy.

5. Conclusion

The number of new oncology drugs is increasing year by year, and clinical studies for their approval should be conducted efficiently. The U.S. FDA has issued the 2001 guidance documents that stipulate situations in which selective safety data collection is acceptable, and indeed has approved at least 10 oncology drug applications on that basis. Selective safety data collection can be an efficient approach to streamline the procedure of clinical studies and should be considered for pivotal clinical studies of oncology drugs, especially for new applications of well-tested drugs.

6. Declaration of Conflicting Interest

The authors declare that there is no conflict of interest with respect to the research, authorship, and/or publication of this article.

7. Disclaimer

Nobuyuki Sekine is an employee of Eli Lilly Japan K. K., but the contents of this article have not been influenced by the company. The author(s) received no financial support for the research, authorship, and/or publication of this article.

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