Original Article

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Analyzing global trends of biomarker use in drug interventional clinical studies

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ABSTRACT: The trend of biomarker use in drug interventional clinical studies was analyzed using *ClinicalTrials.gov* to provide an overview of how biomarkers are used to streamline clinical studies and to examine regional differences. A total of 3,383 clinical study data was analyzed according to phase, region, sponsor, and therapeutic class. The number of clinical studies using biomarkers has been increasing constantly and is dependent on the number of Phase I and II studies. The majority of studies (58.5%) were sponsored by the United States, with the studies being conducted mainly in the sponsor's home region (80.3%). The use of biomarkers was prominent in the oncology area (37.1%). Although current data indicates some bias in the clinical use of biomarkers, it is expected that their use will increase in later phase studies or other therapeutic areas as biomarker development proceeds. In addition, limited regional use of biomarkers may lead to differences in biomarker use in drug development and in combination with political support may result in differences in competitiveness of drug development. Biomarkers would be a powerful tool against deteriorating research and development productivity when used more in appropriate clinical study conditions.

Keywords: Drug development, clinical study efficiency, industrial policy

1. Introduction

Deterioration in drug research and development (R&D) productivity has occurred as a consequence of a dramatic increase in the cost of launching new drugs; a trend that has had a major impact on pharmaceutical companies (*1,2*). Paul *et al*. had reported that the cost to launch one drug was $1,778 million including capital costs (*1*). They showed that the cost incurred in clinical development (Phase I-III) was higher compared with that in the preclinical phase and accounted for 63% of the total cost for each new molecular entity launched. In addition, the cost of clinical studies increased in later phases, with the average out-of-pocket cost for Phase I, II, and III studies to launch one product being $128 million, $185 million, and $235 million, respectively (*1*). Therefore, the impact of clinical study failure, particularly in later phases, is substantial for pharmaceutical companies.

Various methods and tools have been introduced to improve the efficiency and success rate of clinical studies. These approaches were included in the Critical Path Opportunities List published by the Food and Drug Administration (FDA) in 2006 (*3*). Seventy-six items were discussed in the List and were thought to improve the productivity of drug development when they became available. The List included various topics, such as clinical trial design, bioinformatics, and manufacturing, with the number of items related to biomarkers being the largest. Biomarkers are useful for precise diagnosis of diseases, predicting patient outcomes, monitoring disease status and response to treatment, excluding patients potentially vulnerable to drugs, selecting patients who would benefit from drugs, and selecting the appropriate dose for patients. Biomarkers may therefore contribute to the streamlining of R&D. As mentioned above, the cost of clinical studies and impact of study failure is considerable and biomarkers are used to mitigate such impacts. However, it remains unclear how biomarkers are used in clinical studies (*e.g*., phase of studies, study sponsor, and therapeutic area).

Identifying the use of biomarkers in clinical studies may provide information on how biomarkers can contribute to streamlining of clinical studies and how they can be used to increase the effectiveness of these studies. In addition, cross-regional analysis of biomarker use also needs to be considered. As the number of clinical studies varies between regions, the number of clinical studies using biomarkers may also vary

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between regions. Precise analysis may provide future perspectives for drug development and identify strategic differences among regions (*4*).

2. Methods

ClinicalTrials.gov is the biggest clinical study registry, was developed by the US National Institutes of Health (NIH) in collaboration with FDA and was used as the clinical study database in this analysis. A keyword search using "biomarker" (including "marker") was used to obtain a set of data that identified biomarkers with research interest. The data of the studies identified were downloaded into a spread sheet with available field data. XML files of these studies that included more detailed information were also downloaded. To focus on the effects of biomarkers on drug/therapy development, clinical studies using drug (small molecule drugs and biologics for therapeutic use) as a study intervention were further selected using field data. These studies included not only interventional studies, but also a small number of observational studies. Observational studies were therefore eliminated. The selected studies were then stratified according to year (classified by start date), study phase, region of sponsor (US, European Union (EU), Japan or other), funding body (industry, US government, or other), and therapeutic group (classified by condition and intervention). For analysis, Phase I/II and II/III studies were regarded as Phase II and III, respectively. The sponsor's region was classified according to the location information provided. The therapeutic area was selected on the basis of the drug intervention using the therapeutic subgroup (2nd level) of the Anatomical Therapeutic Chemical (ATC) classification system (*5*).

3. Results

A search of clinical studies registered in *ClinicalTrials.gov* identified 40,172 drug interventional studies conducted between 2002 and 2009 (Figure 1). Of these studies, 3,383 studies were identified as the biomarker studies that used any type of biomarker, while the remaining 26,789 studies did not include a biomarker. Biomarker studies were further analyzed.

The number of clinical studies using biomarkers has been increasing year after year, with the proportion of such studies compared to the total number of registered studies also increasing (Figure 2). These studies were then stratified according to their phase. Information on phase was missing in 11.1% of studies, although more than two-thirds of these were considered to be early phase studies based on their study size (< 100 subjects). The number of Phase I and II studies using biomarkers increased steadily, producing 153 Phase I studies and 305 Phase II studies in 2009, and in parallel, the proportion of these studies compared to the total number of corresponding phase studies also increased with time, reaching 11.6% and 13.6% in Phase I and II in 2009, respectively. In contrast, the numbers of Phase III and IV studies using biomarkers increased slightly, producing 71 Phase III studies and 61 Phase IV studies in 2009, although the proportion of these studies compared to the total number of corresponding phase studies remained almost unchanged at around 6% (Figure 3).

When the studies were stratified according to location of the study sponsor it was observed that 58.5% were conducted by US sponsors, 31.5% by EU sponsors, 2.6% by Japanese sponsors, and 7.4% by other sponsors. The number of studies by US sponsor increased steadily,

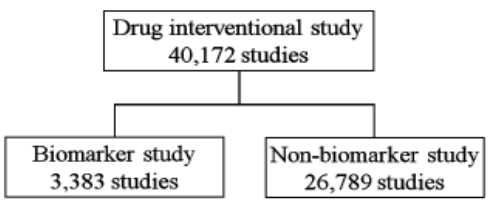

Figure 1. Flowchart showing disposition of biomarker studies for analysis.

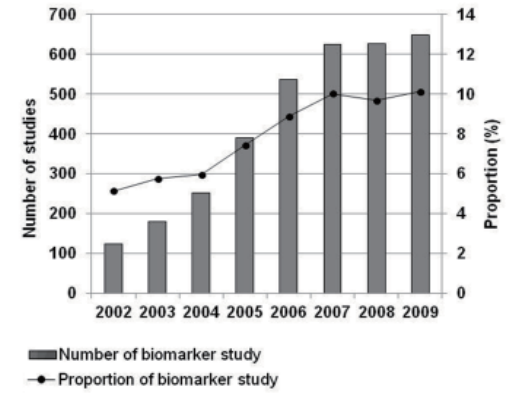

Figure 2. The number and proportion of biomarker studies.

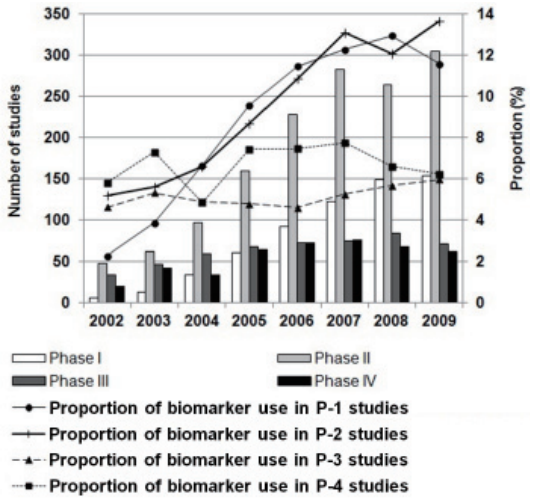

Figure 3. The number and proportion of biomarker studies grouped according to phase.

producing over 400 studies in 2009, while those from EU sponsors also increased until 2007 but slightly decreased in 2008 and 2009 (Figure 4). The number of studies by Japanese sponsors remained low (at most 20 studies) throughout the period. The relationship between sponsor region and study location was analyzed, although study site information was missing in 243 studies. It was found that 80.3% of clinical studies conducted by the US, EU, or Japanese sponsors were conducted in their home country, while 76.9% of biomarker studies were conducted in a single county and 16.1% as multinational studies (Table 1). When this figure was grouped according to sponsor region, different tendencies were observed between the regions, with 10.9%, 25.7%, and 17.0% of US-, EU- and Japanese-sponsored studies being multinational, respectively.

Regarding characteristics of study sponsors, the number of industry funded studies (total 1,620 studies) were more than that of the US government (*i.e.*, NIH, US National Institutes) (total 826 studies), whereas the proportion of biomarker use was higher in US government-funded studies (*e.g.* 13.4% in 2009) than industry-funded studies (*e.g.* 6.0% in 2009) (Figure 5).

Studies were classified into therapeutic subgroups of interventional drugs to analyze biomarker use according to therapeutic areas. As shown in Table 2, the number of clinical studies using biomarkers was notably high for antineoplastic agents (37.1%), followed by lipid modifying agents (6.1%), drugs used in diabetes (5.0%), and drugs for treatment of bone diseases (3.9%) (Table 2). These studies were then classified according to sponsor characteristics and the number of studies was grouped into four major therapeutic subclasses. The US government, US industry, and EU industry funded 826, 853, and 656 studies, respectively; however, when these numbers were divided into therapeutic areas, a different trend was observed (Table 3). The number of clinical studies on antineoplastic agents was high in US government-funded investigations. A similar trend was observed in US industry-funded studies, although the number was relatively low in EU industry-funded studies.

4. Discussion

Our analysis illustrated that researchers have shown an increasing interest in the use of biomarkers in clinical trials over time, with the proportion of such studies compared to total number of studies also rising. This trend may reflect the increase in Phase I and II studies and the fact that biomarkers are used extensively in oncology studies that are predominantly early phase investigations. It has been reported that development of antineoplastic/immunologic agents was the most active of all therapeutic classes (*6*), due to accumulation of knowledge in cancer biology and an associated increase in the number of molecular-targeted medicines. It has also been reported that biomarker use has increased in oncology Phase I studies, with pharmacodynamic markers being used most frequently for the study of the mechanism of action (*7*). Early phase studies tend to

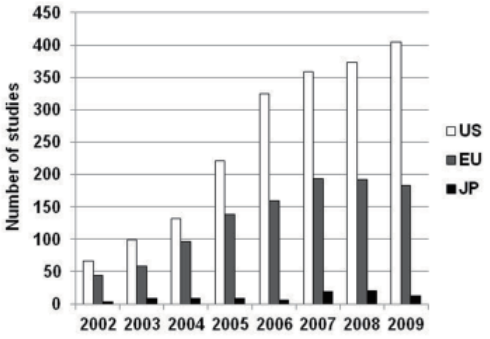

Figure 4. The number of biomarker studies grouped according to sponsor region.

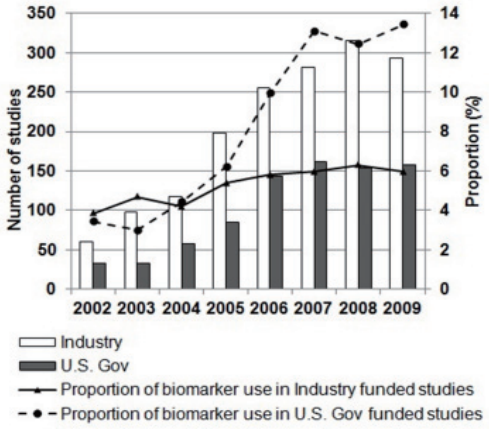

Figure 5. The number and proportion of biomarker studies grouped according to funding by industry or the US government.

Table 1. The number of studies grouped according to sponsor location and type of study

Sponsor location and type of clinical study	US sponsor	EU sponsor	JP sponsor	Total
Single country study in home region	1,522 (76.9%)	539 (50.6%)	31 (35.2%)	2,092 (66.8%)
Single country study outside home region	96 (4.9%)	187 (17.5%)	32 (36.4%)	315 (10.1%)
MNT including home region	190 (9.6%)	232 (21.8%)	1 (1.1%)	423 (13.5%)
MNT outside home region	25 (1.3%)	42 (3.9%)	14 (15.9%)	81 (2.6%)
No site information	145 (7.3%)	66 (6.2%)	10 (11.4%)	221 (7.1%)
	1,978 (total)	1,066 (total)	88 (total)	3,132 (total)

MNT: multinational trial.

Table 2. The number of studies grouped by therapeutic class

ATC2	Therapeutic class	Number of studies
A10	Drugs used in diabetes	168 (5.0%)
A11	Vitamins	79 (2.3%)
B01	Antithrombotic agents	64 (1.9%)
C09	Agents acting on the rennin-angiotensin system	82 (2.4%)
C10	Lipid modifying agents	205 (6.1%)
G03	Sex hormones and modulators of the genital system	83 (2.5%)
J05	Antivirals for systemic use	69 (2.0%)
J06	Immune sera and immunoglobulins	71 (2.1%)
L01	Antineoplastic agents	1,255 (37.1%)
L02	Endocrine therapy	74 (2.2%)
L03	Immunostimulants	92 (2.7%)
L04	Immunosuppressants	97 (2.9%)
M01	Antiinflammatory and antirheumatic products	63 (1.9%)
M05	Drugs for treatment of bone diseases	134 (3.9%)
N06	Psychoanaleptics	66 (2.0%)
R03	Drugs for obstructive airway diseases	82 (2.4%)

ATC classes with less than 50 studies were eliminated.

include biomarkers in oncology and other therapeutic areas, such as pharmacodynamics, pathology, or biomarker exploration, and these collectively contribute to the large number of biomarkers used in Phase I and II investigations. Although use of pharmacodynamic or pathological markers has increased, these markers were usually limited to secondary or exploratory endpoints. Clinical studies using a biomarker as a primary endpoint or patient stratification are still infrequent. This suggests that biomarkers useful for evaluating true endpoints or for selecting patients have not increased to a great extent, and therefore use of biomarkers in later phase studies has not increased. Considering the fact that later stage studies are more costly, development of biomarkers suitable for these studies is necessary to enhance efficiency of clinical studies. Although development of these biomarkers is difficult, FDA recognized the necessity of these biomarkers and efforts have been made to establish some surrogate markers through Critical Path Initiatives. The pharmaceutical industry also understands the importance of predictive markers for patient selection and investigational drugs, and there is now extensive development of these markers, primarily for antitumor agents. FDA also acted in concert with the pharmaceutical industry and released guidelines to support such development activities (*8,9*). The number of these markers is still insufficient, although the number of investigational drugs using patient stratification markers is increasing, mainly in antitumor drug studies. Therefore, the number of biomarkers will definitely increase with the development of pharmacogenomics technology and related regulations and guidelines. These regulations support use of biomarkers, not only in the area of oncology, but also other therapeutic areas and ultimately will help streamline drug development.

Table 3. The number of studies in major therapeutic classes grouped according to funding by industry or the US government

Therapeutic class	US Government	US Industry	EU Industry
Antineoplastic agents	470	333	171
Drugs used in diabetes	28	43	34
Lipid modifying agents	22	61	36
Drugs for treatment of bone disease	5	34	55
Total	826	853	656

The number of biomarker-related clinical studies was highest in the US. This may be due to the US being the largest pharmaceutical market. In addition, US government policies strongly support healthcare-related R&D (*e.g.*, National Cancer Program and Critical Path research). In spite of the large number of clinical studies using biomarkers, the majority of studies were conducted in a single country. The proportion of single country studies is higher than the previously reported rate in North America (54.7%) or Western Europe (27.0%) (*4*). This is due to the majority of studies being relatively small Phase I or II investigations conducted at a small number of investigational sites. In addition, the large number of US government-funded studies conducted mainly in the US also affected this difference. A higher proportion of single country studies also indicates the lower proportion of global studies. The recent study globalization was led by cost constraints; however, it is known that there are ethnic differences in pharmacogenomics in certain cases, and therefore it is reasonable to conduct clinical studies and collect data in home countries to avoid such potential biases (*10*). To utilize biomarkers more efficiently, it is important to collect unbiased data within home countries, *i.e.*, conducting clinical studies within home countries is important to streamline R&D that uses biomarkers. In this context, the situation in Japan is worrisome as the number of biomarker studies is quite small despite Japan being the second largest pharmaceutical market as a single country. As the Japanese regulatory authorities often require clinical data of Japanese patient populations for review and approval, the small number of biomarker studies may lead to a future lag in biomarkers being used in drug development studies, which would be similar to the problem of drug lag in the country (*11*). An example of such biomarker lag is the preclinical renal toxicity markers developed by the Critical Path Institute's Predictive Safety Testing Consortium. These markers were authorized by FDA and European Medicines Agency (EMA) in 2008, whereas Japanese Pharmaceuticals and Medical Devices Agency (PMDA) only authorized these in 2010 (*12,13*). There is a potential risk that biomarker lag may therefore occur in Japan. An increase in the number of clinical studies and use of biomarkers in Japan should be encouraged to avoid this situation.

Finally, while US and EU industries and the US government funded studies more or less equally, the US government funded more oncology studies. The number of oncology studies was substantial compared to other therapeutic areas, with this difference being related to the US healthcare-related policies. National Cancer Institute (NCI) gained the biggest share of the US NIH budget, with the budget for studies including biomarkers constituting almost half of its budget. This trend contributed to the considerable number of early stage oncology studies. In this way, the US government has led the development of biomarkers and the industry has followed. Combined with the aforementioned R&D concentration in home regions, it is likely that the US R&D competitiveness will increase led by the US government, particularly in the field of oncology.

The use of biomarkers has been increasing, although their use is still limited in early phase and oncology studies. Various strategic actions have been implemented to improve this situation, such as investment in the development of biomarkers and preparation of various guidelines for biomarker development. These actions will help biomarker development and streamline clinical studies using biomarkers.

It has also become evident that biomarker use is active in the US, particularly in the field of oncology, mainly due to the US government healthcare-related policies. Collecting data in home regions and implementing policies to support this together with the aforementioned strategies will strengthen the competitiveness of drug development in all countries.

As discussed above, the use of biomarkers has not been sufficient to date. When development of biomarkers proceeds, particularly patient selection markers, this could lead to segmentation of patient populations. Small patient populations could be an obstacle in drug development if streamlining of development is not achieved using biomarkers. Market segmentation may also be a disincentive for pharmaceutical companies even when drugs can be developed using small patient populations. In contrast, provision of safe and effective drugs to small patient populations is necessary from a national perspective of health, and therefore governments also need to play a role in the development and use of biomarkers. The roles of the pharmaceutical industry and government in biomarker development and use are mutually complementary and collaboration between these parties is important for the development of medicine using biomarkers.

Biomarkers would be powerful tools against deteriorating R&D productivity when used more in appropriate clinical study conditions.

Limitation. ClinicalTrials.gov was employed in this research, although due to the nature of this database it is possible that there may be a registration bias. As US is the largest pharmaceutical market and many industries try to first launch their product in this market, many industry-funded studies are registered on this site. US academia and national institutes also register their studies under US Investigational New Drugs (IND), whereas clinical studies conducted by EU or Japanese academia or national institutes may not have been registered on this site. These studies may be covered by other registries such as the Japanese Pharmaceutical Information Center (JAPIC), University Hospital Medical Information Network (UMIN) (Japan), or EudraCT (Europe), although the format of these registries is not unified and therefore integration of this information was not possible. In addition, data before 2004 may be limited as clinical study registration was only encouraged by the International Committee of Medical Journal Editors in 2004 (*14*). Furthermore, there were some cases in which the contents of the study synopsis were not detailed. Therefore, our research could have underestimated the use of biomarkers due to limitations in the keyword search. Further detailed research on the purpose of biomarker use needs to be considered.

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