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ARTICLE

Approval success rates of drug candidates based on target, action, modality, application, and their combinations

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Abstract

The current success rate of a drug candidate, from the beginning of the clinical trial to receiving marketing approval, is about 10%–20%, and it has not changed during the past few decades. Therefore, pharmaceutical companies are under pressure to select one compound, among many others, with a high probability of success. The differences in drug features affect their probabilities of approval success. In this study, we examined the approval success rates of drug candidates, developed in the United States, the European Union, or Japan, by focusing on four parameters ("drug target," "drug action," "drug modality," and "drug application") and their combinations, and identified factors that conditioned the outcome of the drug development process. We obtained a total success rate of 12.8%, after evaluating 3999 compounds. Moreover, after analyzing the combinations of these parameters, the approval success rates of drugs that corresponded to the following categories—a stimulant in drug action or an enzyme in drug target and biologics (excluding monoclonal antibody) in drug modality—were high (34.1% and 31.3%, respectively). Univariate and multivariate logistic regression analyses revealed that stimulant in drug action, and "B" (blood and blood forming organs), "G" (genito-urinary system and sex), and "J" (anti-infectives for systemic use) in drug application were statistically associated with high approval success rates. We found several parameters and their combinations that affected drug approval success rates. Our results could assist pharmaceutical companies in evaluating the probability of success of their drug candidates and, thus, in efficiently conducting the clinical development process.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Differences in drug features affect their probabilities of successful development.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study examined the approval success rates of drug candidates, developed either in the United States, the European Union, or Japan, based on four parameters ("drug target," "drug action," "drug modality," and "drug application") and their combinations, to identify factors that could change the outcome of the drug development.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Approval success rates of drugs with a stimulant as drug action or enzyme as drug target and biologics (excluding monoclonal antibody) as drug modality were high. The multivariate logistic regression analysis showed that a stimulant or "B" (blood and blood forming organs), "G" (genito-urinary system and sex), and "J" (anti-infectives for systemic use) as drug application were statistically associated with high approval success rates.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Our results help pharmaceutical companies to evaluate the approval success of a drug candidate based on the parameters and, thus efficiently advance its clinical development.

INTRODUCTION

The drug research and development process include creating a drug, conducting preclinical and clinical studies, and receiving marketing approval after its regulatory review. This process is associated with an extremely low success rate, ~ 1 in 20,000–30,000.[1] Additionally, the clinical development of a candidate compound, from the start of a clinical trial to marketing approval, has a low success rate (10%–20%) and requires a huge investment that continues increasing year by year, which indicates that the efficiency of this process has been decreasing.[2-11] The success rates to transition between clinical trial phases are different, as the success rate from phase II to III is lower than those from phase I to II and phase III to commercial approval.[7,9,10] Moreover, the approval success rate of a licensed drug candidate is higher than that of a self-originated candidate.[6,9,12] Against this background, pharmaceutical companies are under pressure to select a drug candidate with a high probability of success, among many compounds, and to efficiently conduct the clinical development. Thus, pharmaceutical companies are required to accurately evaluate the probability of success of drug candidates from various points of view.

Drug candidates have various features, and their differences affect the probability that the drug reaches the market.[6-8,10,12-17] For instance, the approval success rates of drugs that target molecules that are not in the host, such as in bacteria and viruses, were much higher than those that target host molecules in vivo.[13] In oncology, the attrition rate of kinase inhibitors is low compared to that of the average of all oncology drugs,[14] possibly because the target and the mechanism of action (MOA) of kinase inhibitors are better known than those of typical cytotoxic drugs, thus improving the selection of patients in clinical trials by using biomarkers.[14] Regarding drug action, although very few studies have reported the relationship between drug action and success rate, among the drugs targeting G-protein-coupled receptors, the approval success rate of the antagonist was slightly higher than that of the agonist.[15] Multiple previous investigations on drug modality have reported that the approval success rates of biologics are higher than those of small molecules.[6-9] Regarding the drug application, the approval success rates of oncology and neurology drugs were low; meanwhile, those of drugs for treating infectious diseases, hematology, and ophthalmology were relatively high.[5,7,8,10,11,16] Because these various parameters influence the approval success rates of the drugs, it is difficult for pharmaceutical companies to estimate the likelihood of the clinical development success. Some companies made a framework based on pharmacological characteristics of drug candidates for improving their success rates,[18,19] but they did not include parameters (e.g., drug target and drug action) of a drug candidate itself. Furthermore, although several studies have been conducted so far, the approval success rates and its definition have greatly differed among them, based on data sources and periods of data collection.

Drugs target diverse molecules in the body, and some drugs have different MOAs but target the same molecule.[20] Thus, their approval success rates may vary, depending on the drug target class and MOA. Previous studies, based on a limited number of compounds, compared the approval success rates between different drug target classes[13] and examined the correlation between the clinical development success or failure and the drug target class.[21] However, the relationship between the drug target and MOA and the probability of success in clinical development has not been investigated based on comprehensive candidate compounds. Santos et al. investigated the distribution of drug target classes of approved and discontinued drugs and the relationship among drug targets, drug modalities, and drug applications, but they did not report approval success rates.[22] Although drug modality is limited to the target molecule (e.g., small molecules can target an intracellular molecule whereas antibodies cannot),[23] the approval success rates of drugs after combining parameters, such as target and modality, have not been determined. Thus,

how the drug features influence the probability of approval success is still poorly understood.

The present study examined the approval success rates of drug candidates, which were developed in the United States, the European Union, or Japan, by focusing on four parameters (drug target, drug action, drug modality, and drug application) and their combinations, and identified factors that conditioned the outcome of the drug development process.

METHODS

Creation of the database

Drug candidates that started phase I trials in the United States, the European Union, or Japan between January 1, 2000, and December 31, 2010, were identified by searching the commercial Pharmaprojects database (Informa) on July 27, 2019. Because the average time of clinical development (from phase I to approval) was reported to be ~ 96.8 months,[4] we set the date of data cutoff on June 30, 2019. Combination products, biosimilars, vaccines, diagnostic products, and compounds in the preclinical stage were excluded from the study.

The following information regarding the selected drug candidates was also extracted from the Pharmaprojects database: generic drug name, drug name, global status, drug disease, drug disease status, therapeutic class, therapeutic class status, MOA, target, target family, and origin.

First, the selected compounds from the Pharmaprojects database were categorized according to the parameter development status, defined as the development stage of the drug candidate with the most progressed indication (Table S1 shows how the obtained information was related to each parameter). Specifically, the compounds were classified into the following categories: phase I, phase II, phase III, succeeded (including launched, withdrawn, registered, and preregistration), and discontinued (including discontinued, no development reported, and suspended). According to Pharmaprojects, the category withdrawn was provided when the drug approval was withdrawn after reaching the market; therefore, we included withdrawn under the succeeded category. In addition, no development reported was defined as the status in which no records of the compound were reported for 1 year, thus drug development was suspected to be discontinued. Therefore, we included the category no development reported under the discontinued category. Because Pharmaprojects grants the category of suspended to a drug development that was temporarily stopped, this category was included under discontinued. Last, compounds under phases I, II, and III, with unclear results were excluded from this analysis.

Later, the remaining compounds were categorized according to four parameters (target, action, modality, and application), based on the information obtained from Pharmaprojects (Table S1) or by searching for public information (including research papers and company press release). If the information regarding a compound was not obtained from any source, it was labeled as not applicable.

Target

Compounds were classified according to their targets into the following categories: receptor, enzyme, ligand, ion channel, transporter, other (proteins related to the cytoskeleton, extracellular matrix, apoptosis, cell cycle, transcription factor, protein degradation, blood clotting, DNA repair, and targeting DNA or RNA), and target unknown (target not identified).

Action (MOA of drug candidate)

Compounds were classified into the following categories: inhibitor, agonist, antagonist, stimulant (target-stimulating agents), other (including enhancer, desensitizer, modulator, scavenger, sensitizer, and stabilizer), and action unknown (MOA not identified).

Modality

Compounds were classified into the following categories: small molecule, monoclonal antibody (mAb), biologics (excluding mAb), and novel modalities (including nucleic acid, cell therapy, gene therapy, and viral medicine).

Application (therapeutic application of drug candidate)

Compounds were classified according to the Anatomical Therapeutic Chemical (ATC) codes,[24] into the following categories: "A" to "V," multiple ATC codes (which corresponded to compounds with multiple therapeutic applications that have progressed to the same development stage), and application unknown (therapeutic application not identified).

Categories "A" to "V" corresponded to: "A" (alimentary tract and metabolism), "B" (blood and blood forming organs), "C" (cardiovascular system), "D" (dermatologicals), "G" (genito-urinary system and sex), "H" (systemic hormonal preparations, excluding sex hormones and insulins), "J" (anti-infectives for systemic use), "L" (antineoplastic and immunomodulating agents), "M" (musculo-skeletal system), "N" (nervous system), "P" (antiparasitic products, insecticides and repellents), "R" (respiratory system), "S" (sensory organs), and "V" (various).

After assigning to each compound a category for all the parameters, only the drugs with complete category information (target, action, modality, and application) were evaluated in this study.

Calculating the approval success rate

The approval success rate (%) was calculated by dividing the number of succeeded compounds by the total number of compounds (both succeeded and discontinued) and multiplying the result by 100. The approval success rates for the four parameters (target, action, modality, and application) and their combinations (target and action, modality and target, and modality and action) were calculated. Regarding the combination of target and action, only action categories considered to work against each target category were used and the rest were classified as others. Compounds without specific category information (other and target/action unknown) were excluded from the analysis for the combination of parameters.

Statistical analyses

We implemented univariate and multivariate logistic regression analyses using the parameter development status (succeeded and discontinued), as a response variable, and the four parameters (target, action, modality, and application), as explanatory variables, to identify factors associated with the outcome of the clinical development. Statistically significant results corresponded to $p < 0.05$. The analyses were performed using StatsDirect software, version 3.2.8 (StatsDirect Ltd).

RESULTS

Out of 5681 initial drug candidates that started their clinical development between January 1, 2000, and December 31, 2010, in the United States, the European Union, or Japan, 813 compounds met the exclusion criteria, thus they were removed from the analysis. Next, the parameter development status was applied to the remaining 4868 compounds (Figure 1 and Table S2). After eliminating 673 compounds under development (phases I, II, and III), which contained unclear results, the remaining 4195 compounds were classified according to 4 parameters (target, action, modality, and application; Table S3). Finally, 196 compounds, including at least one not applicable category in any of the parameters, were excluded, resulting in 3999 compounds that were evaluated in the present study (Figure 1). Overall, the numbers of compounds under the succeeded and discontinued categories were 513 and 3486, respectively, and the approval success rate in total was 12.8%.

The approval success rate associated with each parameter is shown in Figure 2. Regarding the target parameter, the success rates of ligand and target unknown categories were the lowest, 5.4% and 5.5%, respectively (Figure 2a). Regarding success rates related to the action parameter, agonist and stimulant categories had higher rates than those of antagonist and inhibitor (Figure 2b). However, the success rate of the category action unknown was the lowest. When analyzing the modality parameter, the success rate of the biologics (excluding mAb; 15.2%) category was the highest, followed by those of small molecules (13.0%) and mAb (10.7%) categories, and last by that of novel modalities category with lowest rates (Figure 2c). Regarding the application parameter, success rates of "B," "G," "J," and "S" categories were high (Figure 2d). In contrast, the success

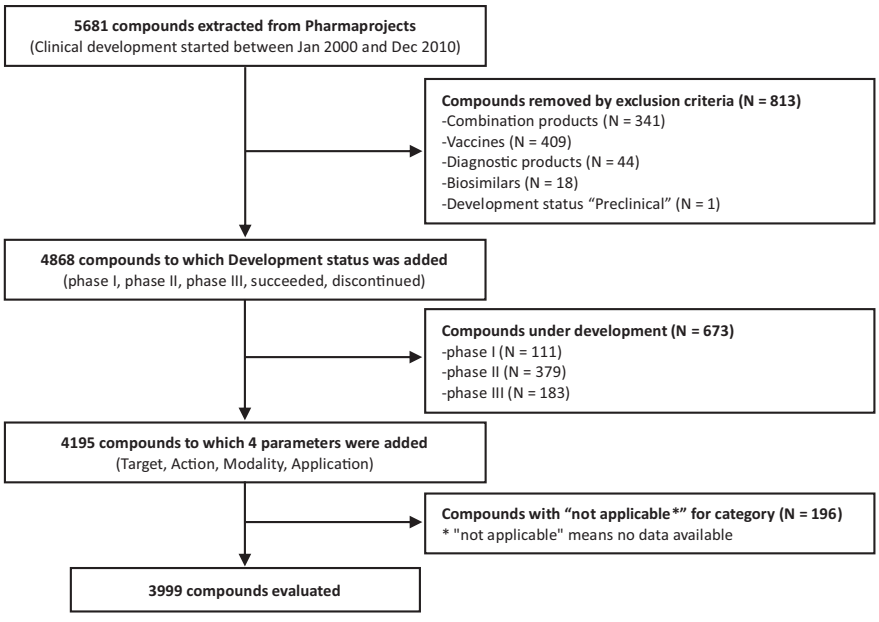

FIGURE 1 **Database creation**. N, number of compounds

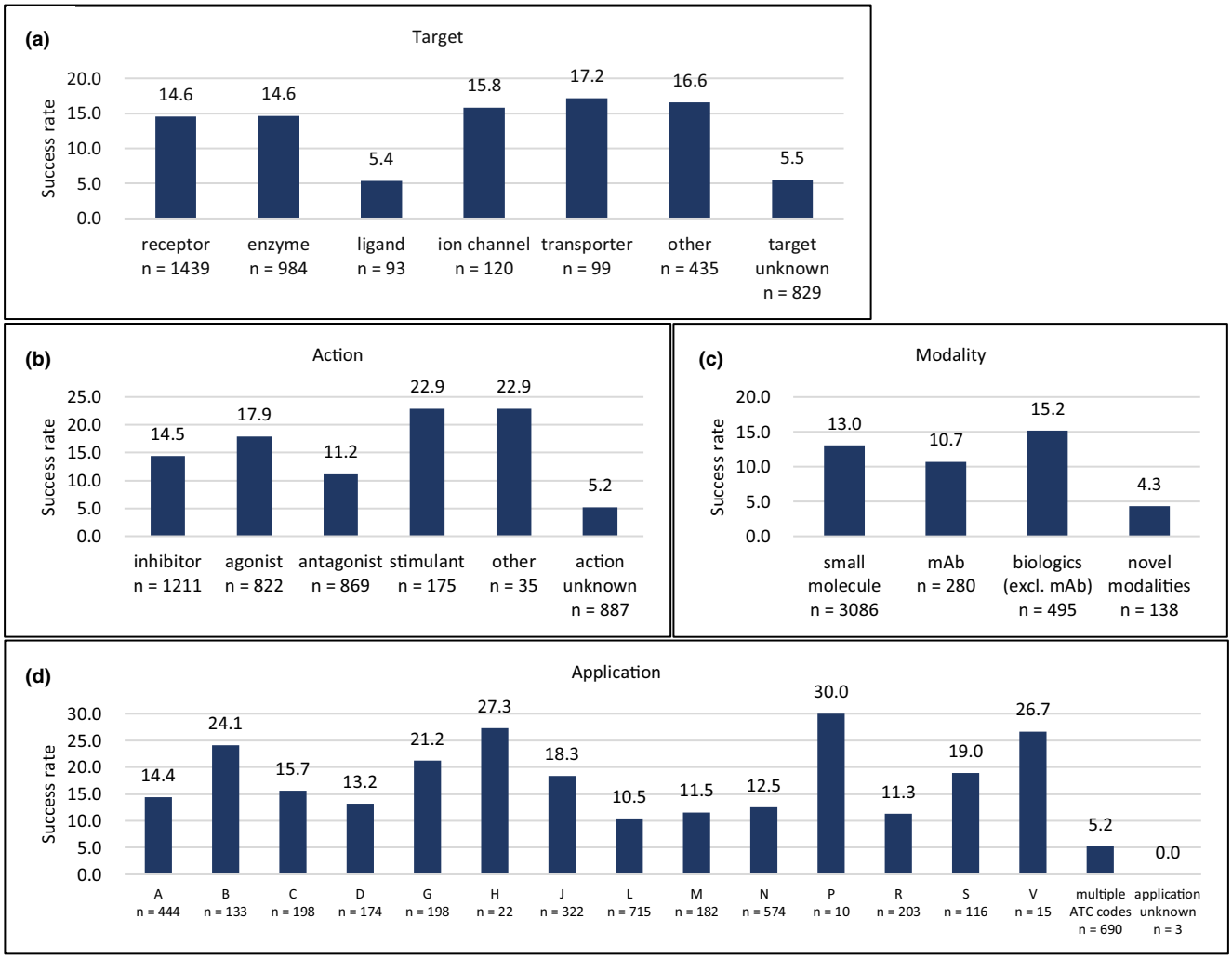

FIGURE 2 **Comparison of approval success rates for target, action, modality, and application parameters.** Success rates of (a) different targets. The category other included compounds targeting proteins related to the cytoskeleton, extracellular matrix, apoptosis, cell cycle, transcription, protein degradation, blood clotting, and DNA repair or targeting DNA or RNA. Target unknown was defined as not target identified, (b) different actions. The category other included enhancer, desensitizer, modulator, scavenger, sensitizer, and stabilizer. Action unknown: the mechanism of action of the compound was not identified, (c) different modalities. Monoclonal antibodies (mAbs), the category novel modalities included nucleic acid, cell therapy, gene therapy, and viral medicine, (d) different applications. "A" (alimentary tract and metabolism), "B" (blood and blood forming organs), "C" (cardiovascular system), "D" (dermatologicals), "G" (genito-urinary system and sex), "H" (systemic hormonal preparations, excluding sex hormones and insulins), "J" (anti-infectives for systemic use), "L" (antineoplastic and immunomodulating agents), "M" (musculo-skeletal system), "N" (nervous system), "P" (antiparasitic products, insecticides and repellents), "R" (respiratory system), "S" (sensory organs), "V" (various), and multiple Anatomical Therapeutic Chemical (ATC) codes, which corresponded to compounds with multiple therapeutic applications that have progressed to the same development stage, application unknown: not identified application, *n*, number of compounds

rates of the categories "L," "M," "N," and "R" were lower than the total approval success rate (12.8%). Moreover, the success rate of the multiple ATC codes category was the lowest.

Table 1 shows the approval success rates for the combinations of parameters. Analysis of the combination of target and action parameters revealed that the success rates of the combinations enzyme and stimulant ($n = 94$, 23.4%) and ion channel and agonist ($n = 28$, 21.4%) were the highest (Table 1). Among the compounds targeting ligand, antagonist was the only action parameter with success. Among the compounds targeting receptor or ion channel, the approval success rate of agonist were ~ 7% points higher than those of antagonist. For the combination of modality and target parameters, the combination of biologics (excluding mAb) and enzyme ($n = 64$, 31.3%) resulted in a high approval success rate (Table 1). Among the compounds targeting ligand, mAb ($n = 56$, 7.1%) and biologics (excluding mAb, $n = 15$, 6.7%) were the only modality parameters with success. The combination of mAb and receptor was associated with a higher approval success rate of 13.9%, compared to the overall success rate of mAb (10.7%). For the combination of

TABLE 1 Approval success rates for combined parameters: target and action, modality and target, and modality and action

Target and action	Target											
	Receptor		Ion channel		Enzyme			Ligand			Transporter		
Action	Total[a]	Success rate (%)	Total	Success rate (%)	Action	Total	Success rate (%)	Action	Total	Success rate (%)	Action	Total	Success rate (%)
Agonist	772	18.0	28	21.4	Stimulant	94	23.4	Antagonist	65	7.7	Inhibitor	81	19.8
Antagonist	604	10.9	89	14.6	Inhibitor	870	13.9	Inhibitor	26	0.0			
Others[b]	42	9.5	1	0.0	Others[b]	8	12.5	Others[b]	1	0.0	Others[b]	15	6.7

Modality and target	Target									
	Receptor		Enzyme		Ligand		Ion channel		Transporter	
Modality	Total	Success rate (%)	Total	Success rate (%)	Total	Success rate (%)	Total	Success rate (%)	Total	Success rate (%)
Small molecule	1063	15.4	871	13.8	13	0.0	117	16.2	93	18.3
mAb[c]	101	13.9	24	12.5	56	7.1	1	0.0	3	0.0
Biologics (excl. mAb)	239	13.0	64	31.3	15	6.7	2	0.0	2	0.0
Novel modalities[e]	36	2.8	25	4.0	9	0.0	0	NA[d]	1	0.0

Modality and action	Action							
	Inhibitor		Agonist		Antagonist		Stimulant	
Modality	Total	Success rate (%)	Total	Success rate (%)	Total	Success rate (%)	Total	Success rate (%)
Small molecule	1056	15.2	587	20.1	668	11.4	64	14.1
mAb	73	8.2	8	0.0	135	11.9	2	0.0
Biologics (excl. mAb)	42	14.3	200	13.5	46	10.9	88	34.1
Novel modalities	40	7.5	27	7.4	20	0.0	21	4.8

Abbreviations: mAb, monoclonal antibody; NA, not applicable.

[a]Total number of compounds.

[b]Action categories without considered to work against each target category.

[c]Monoclonal antibody.

[d]Calculation is not applicable.

[e]Including nucleic acid, cell therapy, gene therapy, and viral medicine.

TABLE 2 Results of univariate and multivariate logistic regression analyses

		Univariate logistic regression analysis			Multivariate logistic regression analysis		
*$P < 0.05$	Category	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Target	Receptor	Reference			Reference		
	Enzyme	1.00	0.80–1.26	0.98	0.94	0.57–1.57	0.82
	Ligand	0.33	0.13–0.83	0.02*	0.48	0.18–1.27	0.14
	Ion channel	1.10	0.66–1.84	0.71	1.52	0.88–2.63	0.13
	Transporter	1.21	0.71–2.09	0.48	1.39	0.69–2.79	0.36
	Other	1.16	0.87–1.55	0.32	1.23	0.78–1.94	0.37
	Target unknown	0.34	0.25–0.48	<0.01*	0.80	0.36–1.79	0.58
Action	Inhibitor	Reference			Reference		
	Agonist	1.29	1.01–1.64	0.04*	1.43	0.85–2.41	0.18
	Antagonist	0.74	0.57–0.97	0.03*	0.85	0.53–1.38	0.52
	Stimulant	1.75	1.19–2.58	0.005*	1.89	1.20–2.97	0.006*
	Other	1.75	0.78–3.92	0.17	2.46	0.91–6.59	0.07
	Action unknown	0.32	0.23–0.45	<0.01*	0.37	0.18–0.78	0.01*
Modality	Small molecule	Reference			Reference		
	mAbs	0.80	0.54–1.19	0.27	1.12	0.72–1.76	0.62
	Biologics (excl. mAb)	1.19	0.91–1.56	0.20	0.83	0.61–1.15	0.27
	Novel modalities	0.30	0.13–0.69	0.005*	0.26	0.11–0.60	<0.01*
Application	A	Reference			Reference		
	B	1.88	1.17–3.03	0.01*	1.75	1.06–2.88	0.03*
	C	1.10	0.69–1.76	0.68	1.05	0.65–1.71	0.83
	D	0.90	0.54–1.51	0.70	1.25	0.73–2.12	0.42
	G	1.60	1.04–2.46	0.03*	1.57	1.01–2.46	0.047*
	H	2.23	0.84–5.90	0.11	2.15	0.78–5.93	0.14
	J	1.33	0.90–1.96	0.15	1.70	1.12–2.58	0.013*
	L	0.70	0.49–0.99	0.046*	0.80	0.54–1.19	0.27
	M	0.77	0.46–1.31	0.34	0.88	0.51–1.50	0.63
	N	0.85	0.59–1.22	0.38	0.81	0.56–1.18	0.28
	P	2.54	0.64–10.10	0.18	3.61	0.82–15.79	0.09
	R	0.76	0.46–1.26	0.29	0.77	0.46–1.29	0.32
	S	1.39	0.81–2.37	0.23	1.55	0.89–2.69	0.12
	V	2.16	0.67–6.99	0.20	2.73	0.79–9.44	0.11
	Multiple ATC codes	0.33	0.21–0.50	<0.01*	0.32	0.21–0.49	<0.01*
	Application unknown	<0.01	<0.01–>100	0.97	0.01	<0.01–>100	0.77

Abbreviations: A, alimentary tract and metabolism; ATC, Anatomical Therapeutic Chemical; B, blood and blood forming organs; C, cardiovascular system; D, dermatologicals; G, genito-urinary system and sex; H, systemic hormonal preparations, excluding sex hormones and insulins; J, anti-infectives for systemic use; L, antineoplastic and immunomodulating agents; M, musculo-skeletal system; mAb, monoclonal antibody; N, nervous system; NA, not applicable, P, antiparasitic products, insecticides and repellents; R, respiratory system; S, sensory organs; V, various.

*$p < 0.05$.

modality and action, combinations of small molecules and agonist ($n = 587$, 20.1%), and biologics (excluding mAb) and stimulant ($n = 88$, 34.1%) resulted in high approval success rates (Table 1).

Table 2 shows the different parameters associated with the clinical development outcomes. Categories that statistically, significantly affected the approval success rates according to the univariate logistic regression analysis were: ligand and target unknown under target parameter (reference: receptor), agonist, antagonist, stimulant, and action unknown under action parameter (reference: inhibitor), novel modalities under modality parameter (reference: small molecule), and "B,"

"G," "L," and multiple ATC codes under application parameter (reference: A [Alimentary tract and metabolism]; Table 2). As a result of the multivariate logistic regression analysis, four factors were associated with high approval success rates: stimulant under action, and "B," "G," and "J" under application, and three factors were associated with low approval success rates: action unknown under action, novel modalities under modality, and multiple ATC codes under application (Table 2).

DISCUSSION

In the present study, we calculated the approval success rates of drug candidates that started their clinical development between 2000 and 2010 in the United States, the European Union, or Japan, based on four parameters (target, action, modality, and application) and their combinations. As a result, we found several parameters and their combinations that affected drug approval success rates. It should be noted that, in the present study, probability of success by drug action and those by the combinations of the parameters were identified, which have not been fully studied so far.

We used the final outcome of the clinical development for calculating the drug approval success rates, as previously defined by Shih et al.[13] Although they included compounds that were withdrawn under the discontinued category, we included such compounds in the succeeded category because they received approval once. Additionally, many previous studies focused on the success rate of each phase transition (phase I to II, phase II to III, and phase III to approval),[5-11,14] but others used the final results of development.[13,22] In addition, the definitions and calculation methods of the success rates were various. In our study, the approval success rates were focused on the final outcome of the clinical development process rather than on the phase transition. Because the approval success rate obtained in the present study (12.8%) was similar to that reported by previous studies, which used data from similar periods as ours, we considered that our calculation of the approval success rate was valid.

Although some studies have investigated how target classes of drug candidates affected the drug discovery effectiveness,[13,21,22] few have focused on ligands. Santos et al. classified and compared drug targets in their ability to condition the approval of compounds, but they did not include ligands in their classification.[22] In our study, the approval success rate of the ligand was lower than those of other targets (Figure 2a), according to the univariate logistic regression analysis; however, the association was not confirmed in the multivariate analysis (Table 2). Ligands transduce the signal intracellularly by binding to their receptors after being secreted extracellularly, but other target molecules (receptor, ion channel, and transporter) are localized at the plasma membrane.[25-28] Therefore, we assumed that targeting a ligand is hard to control because the compounds need to catch the molecule extracellularly released,[28,29] thus the determination of the proper compound doses is difficult to perform. However, there is a possibility to increase the success rates of ligands by combining genetic insight, because Nelson et al. reported that success rates in clinical development of genetically validated targets were twice higher than those of not validated targets.[30]

We confirmed that the approval success rate of stimulant was highest in action, and stimulant was associated with high approval success rate from the result of multivariate analysis (Figure 2b, Table 2). The approval success rate of a combination of stimulant or enzyme and biologics (excluding mAb) was also high (Table 1). Many of these combinations, including stimulant, corresponded to compounds supplementing enzyme and other substances that were not produced or functionally deficient in vivo. Because such compounds supplement functions in vivo, their responses and effects may be more easily predicted than other actions, and thus they may be more likely to succeed in their marketing approval. Regarding biologics, their structures are similar to molecules in vivo and their approval success rates are higher than those of small molecules,[6-9] which may lead to higher approval success rates when combined with a stimulant.

Regarding agonist and antagonist, which are reciprocal in actions, both of them were not statistically significant in the multivariate analysis, but the result of the univariate analysis suggested that agonist was associated with high approval success rate and antagonist was associated with low approval success rate (Figure 2b, Table 2). Although agonists activate target molecules and function similarly during in vivo signal transduction, antagonists work antagonistically.[31] Hence, we think the approval success rate of the antagonist was low because it is difficult to predict the response of compounds acting as antagonist.

Under the modality category, biologics (excluding mAb) had the highest approval success rates, which was concordant with multiple previous studies.[6-9] One of them reported that the approval success rates of mAb were higher than those of small molecules,[7] in contrast to our results. The contrariety in results could be attributed to differences in the period of data collection and/or the method for calculation of the approval success rates. Reichert et al. reported no difference in approval success rates between small molecules and mAbs in the oncology area.[32] Therefore, it would be important to discuss not only modality but a combination of modality and application in creating a clinical development strategy.

In addition, our results indicated that the approval success rates of novel modalities, including nucleic acid, cell therapy, gene therapy, and viral medicine, were low, according to the multivariate analyses (Figure 2c, Table 2). Because the clinical development of drugs that have these modalities has

been increasing recently, we believe that many of these drug candidates were not included in our data collection period. Thus, different results might be obtained when considering more recent data.

Regarding applications (ATC codes), we determined that the approval success rates of "B," "G," and "J" were high, as indicated by the multivariate analysis (Figure 2d, Table 2), similarly to many previous studies.[6-8,10,11,16] One of reasons for which "B" and "J" approval success rates were high could be due to the fact that their molecular mechanisms are better known, and thus their clinical development are easier to perform than those of other applications. The approval success rate of the "L," which included many oncology and a few immunological compounds, was low as indicated by the univariate analysis (Figure 2d, Table 2), in agreement with multiple studies.[7,10] Although we calculated the approval success rates of compounds for each therapeutic application based on the ATC code, analyses of the success rates of compounds that can treat individual diseases may be able to reveal more specific features.

Our results showed that the approval success rates of compounds with target unknown and action unknown were low, and this result was confirmed for the category action unknown by the multivariate analysis (Figure 2, Table 2). We understand that the status of target unknown and action unknown indicates that the drug candidate itself and its in vivo behavior are not well understood. Difficulties in determining its usage, dose, and therapeutic application may challenge its clinical development. Moreover, considering that the approval success rates of multiple ATC codes were low when the application was not focused on a specific therapeutic area, the examination of strategies for the clinical development of a drug that targets each disease would be inadequate, making their clinical development difficult.

There are several limitations to our research. We only analyzed drug candidates that clinical development processes began between 2000 and 2010, and we could not examine older or newer compounds outside the period. Second, although we conducted a thorough visual check and review of the extracted data, data accuracy is dependent on the quality of the Pharmaprojects database. Furthermore, we could not precisely investigate compounds that were discontinued because some of these data were not published by the companies. We believe that a more detailed analysis and interpretation of each factor are needed. Moreover, the confirmation of our results by using more various databases in the future is also needed.

In conclusion, we revealed how categories in the four parameters (target, action, modality, and application) and their combinations affected the outcome of the clinical development process and thus the approval success rates of the compounds. We believe that our results will be useful for pharmaceutical companies to evaluate the probability of success of a drug candidate based on the parameters and efficiently conduct the clinical development.

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CONFLICT OF INTEREST

Shingo Yamaguchi is an employee of GlaxoSmithKline K.K., Tokyo, Japan. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

S.Y., M.K., and M.N. wrote the manuscript and designed the research. S.Y. performed the research and analyzed the data.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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