Pharmaceutical Probability of Success

Critical strategic decisions are made based on valuation models of pharmaceutical assets. Of the many assumptions that underpin a valuation model, probability of success is a key input, but one that often receives little thought or consideration. Several publications have analyzed historic probability of success in the pharmaceutical industry. Each study uses different datasets or different methodologies, often leading to a significant difference in conclusions. We examine the literature, provide a summary of the different datasets and urge model developers to think carefully about which assumptions to use. Depending on the profile of the drug, there can be as much as a 280% difference for the final valuation. Failing to account for the characteristics of the molecule, which we believe is best done with a thorough review of the data by seasoned drug developers, can result in a significantly skewed picture of valuation and misguided investment decisions.

By Serena Zhou and Rob Johnson

About the Authors

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Introduction

The estimated cost of developing pharmaceutical drugs has increased from $1.04 billion in the 1990s through the mid-2000s to $2.56 billion in the 2000s through the mid-2010s[1]. One primary factor of this increase in cost is the risk associated with bringing a drug from preclinical into the clinic and ultimately to market. Much of this uncertainty comes from the likelihood, higher in some indications and lower in others, that the drug in development may be terminated due to any number of factors, including efficacy, safety, or commercialization concerns[2]. These drug development risks must be considered when performing pharmaceutical valuations for companies and products, as they comprise a basis of the industry standard risk-adjusted net present value (rNPV). For pharmaceutical valuations, an understanding of the historical probability of success of a therapeutic through to approval provides an understanding of whether an investment is in a company's strategic interest.

This report provides a review of the published literature and their methodologies on the pharmaceutical probabilities of success from 1993 to 2015 and insight into any potential trends that have emerged in the past 22 years.

Executive Summary

This whitepaper summarizes the probabilities of success from eight publications reviewing therapeutic products from 1993 to 2015. While differences in years covered, methodology, and sample source did result in differences between the various publications, several general trends emerged.

Of the four stages of clinical development, Phase II to Phase III had the lowest probability of success because it is the first stage during which efficacy is assessed. While efficacy and safety are two of the primary reasons for clinical trial termination, commercial reasons such as rationalization of the company portfolio also play an important role in the low probability of success values, affecting as many as a third of all trials terminated in Phases I and II from 2005 to 2010. Of the 16 major therapeutic areas covered by the publications, psychiatry and oncology had the lowest overall probabilities of success, although only five indications exceeded an overall likelihood of approval (LOA) of one in five.

Further breakdowns to determine the role of a lead indication demonstrate that while lead indications typically have improved success when considering Phase III to Approval and overall LOA, there are inconsistent effects elsewhere, particularly in Phases I to III. Oncology, one of the largest therapeutic classes and consisting of up to as much as a third of the data evaluated by some publications, has a large role in decreasing the overall probability of success values often reported without differentiating by therapeutic area. Among oncological tumor types, hematological tumors had lower probabilities of success in Phase I, owing to greater safety risks, but solid tumors had lower probabilities of success in Phases II, III, and Registration to Approval, most likely due to the issues of tumor penetration, toxicity, and mechanistic insufficiency.

Other trends were present when considering orphan indications, biomarker usage, modalities, and drug origin. Orphan indications' probability of success was inconsistent in terms of Phase III to Approval and overall probability of success with the various sources differing on whether orphan indications improved the likelihood of approval. In contrast, biomarkers for patient selection improved probability of success across all clinical stages but resulted in a decrease in metabolic and endocrinology indications due to the low sample sizes. When biomarker identification and evaluation trials are included, biomarker usage did not cause a large and consistent increase in the probability of success.

Among the various drug classes or modalities, NMEs had the lowest probability of success, but when oncology and non-oncology modalities were considered, oncology vaccines had by far the lowest overall LOA. Products that were licensed-in to a top 50 pharmaceutical firm had higher probabilities of success than both self-originated and

licensed-out, demonstrating the importance of partnering to the advancement of clinical programs for patients.

Clear understanding of the orphan or biomarker status and careful selection of a probability of success value will enable the development of valuations more in line with the true value of a proposed drug.

Methods and Materials

Eight papers, published since 2010 and including data from 1993 to 2015, were reviewed as part of this paper. In the literature search, preference was given to those papers that provided breakdowns by various areas of interest, such as indications, oncological indications, biomarker usage, and compound origin, as well as those that encompassed a large breadth of years and a large set of compounds. For those authors that have published extensively on the subject, the most recent publications on the subject were selected. **Table 1 – Differences between Sources** provides a summary of the differences between the papers used:

Table 1 – Differences between Sources

Error! Reference source not found. – Differences between Sources					
Publication	**Affiliation**	**Years**	**Compounds**	**Data Source**	**Companies/Trials**
DiMasi et al, 2010	Tufts University	1993-2004	1,738	IMS R&D database	Top 50 pharmaceutical companies (by sales)
Paul et al, 2010	Eli Lilly	Through 2007	Unknown	KMR Group, Eli Lilly R&D pipeline data	13 large pharmaceutical companies
Hay et al, 2014	BioMedTracker	2003-2011	4,451	BioMedTracker	835 companies
Smietana et al, 2015	McKinsey & Company	2007-2012	Unknown	Informa Pharmaprojects	All novel compounds
DiMasi et al, 2016	Tufts University	1995-2007	1,442	IMS R&D Database	Top 50 pharmaceutical companies (by sales)

Smietana et al, 2016	McKinsey & Company	1996-2014	9,200+	Informa Pharmaprojects	Unknown
Thomas et al, 2016	BIO & Amplion	2006-2015	7,455	BioMedTracker	1,103 companies
Wong et al, 2018	Massachusetts Institute of Technology (MIT)	2000-2015	21,143	Informa Trialtrove and Pharmaprojects	185,994 trials from industry and non-industry

All figures were generated with PowerBI (**Figure 2**), Rawgraphs.io (**Figure 3**), or DataWrapper (all other figures).

Overall Success Rates and Trends

For products evaluated prior to Phase I, it is important to include the discovery and preclinical success rates of the product. The success rates prior to Phase I were described by Paul et al (2010), based on data from 13 major pharmaceutical companies and the Eli Lilly internal R&D pipeline:

Table 2 – Probability of Success before Phase I

Table 2 – Success Rates before Phase I				
Source	**Target to Hit**	**Hit to Lead**	**Lead Optimization**	**Preclinical**
Paul et al, 2010	80%	75%	85%	69%

Estimates of 61%, 38%, 63%, and 89% can be used as benchmarks for the probability of success for Phase I, Phase II, Phase III, and Approval, respectively, for all indications and drug classes, with an overall success rate of 13%, as based on a review of 8 publications encompassing data from 1993-2015:

Figure 1 – Historical Overall Probability of Success

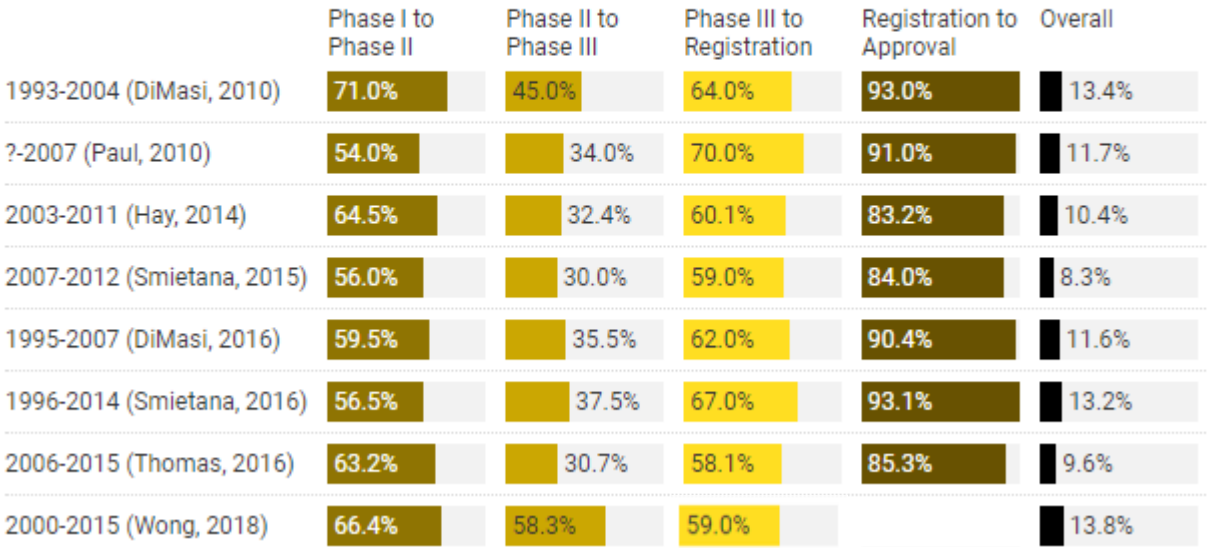

Figure 1. Overall Probability of Success from Eight Major Publications and their Probability of Success Ranges for 1993 to 2015. *Wong et al (2018) reports only Phase III to Approval values and does not separate Phase III to Registration and Registration to Approval. The reported value for Phase III to Approval for Wong et al (2018) for all indications is 59%, which is listed under Phase to Registration in* Figure 1. *Whenever Wong et al (2018) is a source of information, Phase III to Approval is included as well, in addition to Phase III to Registration and Registration to Approval.* [2,3,4,5,1,6,7,8]

In the years (1993-2004) described by DiMasi et al (2010), the Phase I and Phase II success rates (75% and 45%) were higher than many of the more recently published papers. Several factors may contribute to the increase in Phase I failures, including an increased prioritization of pipeline assets that subsequently results in more compounds failing in Phase I rather than in the costlier Phase II and Phase III[6].

The methodology of Wong et al (2018) differs from most of the prior publications, described in more detail in **Appendix: Source Methodology**, which may account for its higher success rates in Phase II, Phase III to Approval, and overall likelihood of approval relative to other publications after DiMasi et al (2010). Nonetheless, the success rates have stayed largely consistent since the start of the 21st century.

Based on the benchmark success rates, it is possible to determine how many compounds would be required in each phase of development to reach a commercial launch:

Figure 2 – Number of Assets Needed for One Launch, per Development Phase

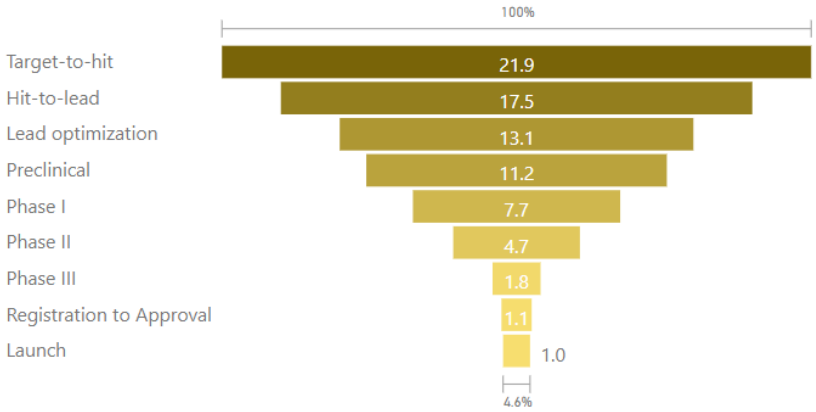

Figure 2. Number of Assets Needed for One Launch, by Development Phase, starting with Target-to-Hit.
The number of assets required for each development phase to reach one launched product are calculated from probabilities of success prior to Phase I (as reported by Paul et al (2010) and summarized in Table 2*) and the average benchmark values for each clinical stage, as calculated from values in* **Error! Reference source not found.**. *For one product launch, about 22 assets are required in the target-to-hit stage.*

The importance of a correct probability of success value for an indication is highlighted in **Figure 3**, as the potential values for each phase's probability of success varies greatly:

Figure 3 – Overall Distribution for Probability of Success

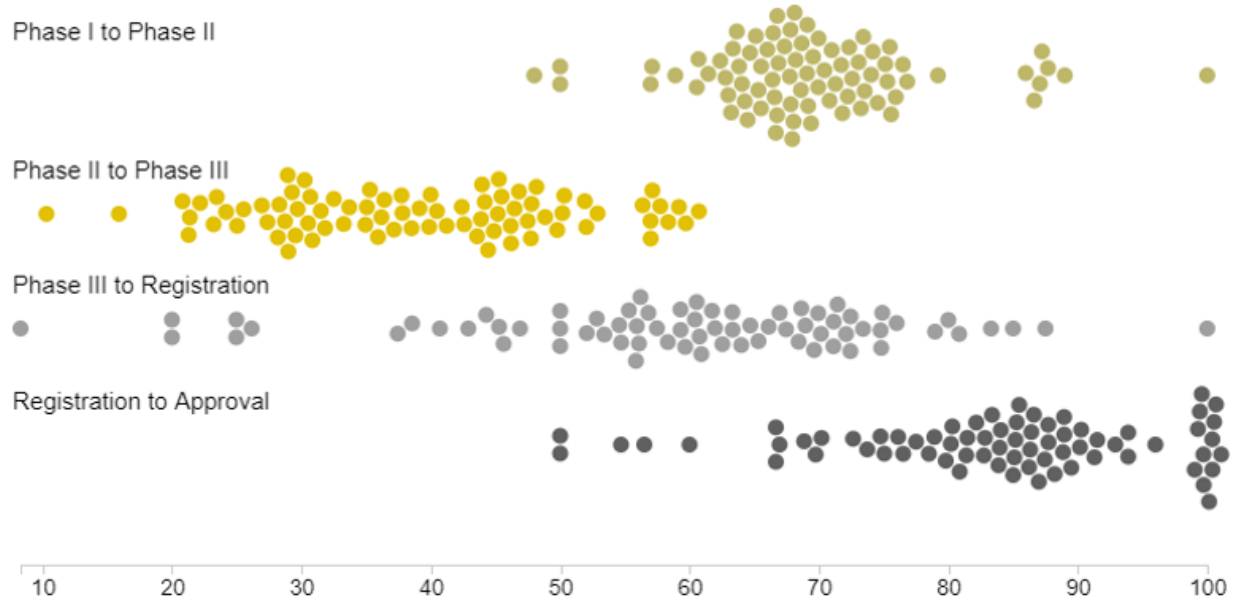

Figure 3. Overall Distribution for Each Phase of Clinical Development.
Data presented was compiled from all eight sources, as described in Error! Reference source not found.*, across all indications, lead indications, drug classes, and other probability of success breakdowns as reported throughout this whitepaper. Phase I to Phase II probability of success has a range of 48% to 100% (n=80). Phase II to Phase III probability of success has a range of 10% to 61% (n=80). Phase III to Registration probability of success has a range of 8% to 100% (n=72). Registration to Approval has a probability of success range of 50% to 100% (n=71).*

Phase II has the lowest probability of success distribution, as it is the first stage during which efficacy is evaluated. While program termination in Phase I and Phase II may

indeed be due to toxicity or poor efficacy, there is also the considerable likelihood of a project termination at these phases due to commercial or strategic reasons:

Table 3 – Alternative reasons for Phase I and Phase II Termination

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Reason for termination	**Phase I**	**Phase II**
"Rationalization of company portfolio"	18.5%	21.3%
"Commercial"	6.4%	4.5%

Table 3. Alternative Reasons for Phase I and Phase II Termination.
The data is taken from Waring et al (2015) and details the leading reasons other than toxicity or poor efficacy for early clinical stage program termination. Waring et al (2015) reviewed 812 compounds from AstraZeneca, Eli Lilly, GlaxoSmithKline, and Pfizer from 2000 to 2010[9].

In fact, there has been an increase between 2000-05 and 2005-10 in terms of the termination of assets in Phases I and II due to "rationalization of company portfolio" and "commercial", which could contribute to the overall decrease in Phase I and Phase II success rates seen since 2003:

Table 4 – Difference between 2000-05 and 2005-2010

Table 4 – Difference in Alternative Reasons between 2000-05 and 2005-2010		
Reason for termination	**2000-05**	**2005-10**
"Rationalization of company portfolio"	12.7%	32.1%
"Commercial"	6.4%	7%

Table 4. Comparison of Alternative Reasons between 2000-2005 and 2005-2010
The data is taken from Waring et al (2015) and details the change from the first half of the 2000-2010 decade to the second half of the decade. "Rationalization of company portfolio" experienced an increase of 19.4% within the period while "commercial" reasons increased only 0.6%.

Due to these alternative reasons for program termination, it may be prudent to adjust the Phase I and Phase II success rates accordingly, as the reported values do not differentiate based on the reasons for termination. Additionally, Hay et al (2014) found that18% of 359 Phase III trial suspensions were due to commercial reasons as opposed to lack of efficacy or safety.

The subsequent sections will break up these pharmaceutical probability of success values by therapeutic class, lead indication, oncological indication, orphan and rare

disease indication, biomarker status, drug class, and source of asset, and discuss these relative success rates and their effect on a valuation model.

Probability of Success by Therapeutic Area and Lead Indication

The target indication of the asset is an important consideration for any valuation. **Error! Reference source not found.** displays the average probability of success for each phase for 16 major therapeutic areas:

Figure 4 – Average Probability of Success by Therapeutic Area

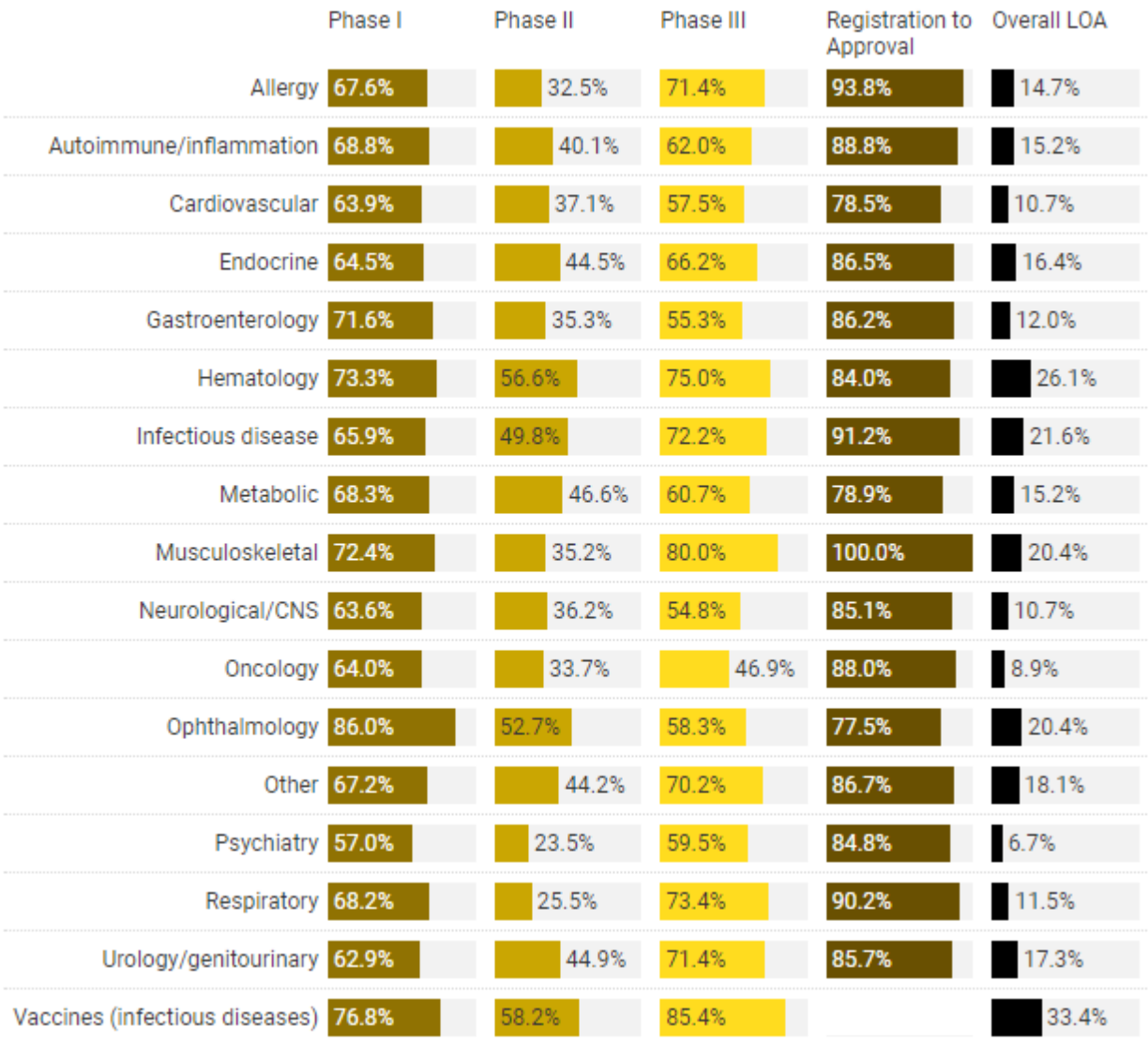


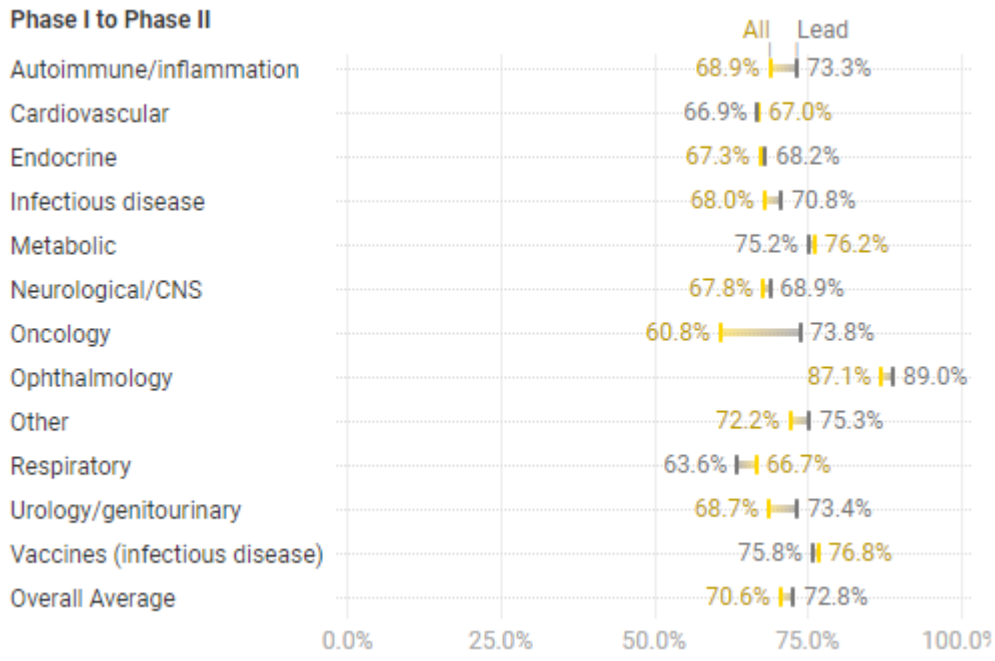
Figure 4. Average Probability of Success by Therapeutic Area from Phase I to Approval.
Data averaged from results from Wong et al (2018), Thomas et al (2016), Hay et al (2014), and DiMasi et al (2010). For several indications, only one or two of the papers reported values, as in allergy and hematology (only reported by Thomas), musculoskeletal (only reported by DiMasi), vaccines for infectious disease (reported only by Wong), gastroenterology (reported by both Thomas and DiMasi), ophthalmology (reported by Wong and Thomas), psychiatry (reported by Thomas and Hay), and urology/genitourinary (reported by Wong and Thomas). Likelihood of approval is abbreviated as LOA. Vaccines, reported only by Wong et al (2018) as a disease area rather than drug class, lacks a Registration to Approval value, as Wong et al (2018) only reports Phase III to Approval data (listed in this Figure as Phase III to Registration).

Of the 16 therapeutic areas, psychiatry had the lowest probability of success for Phase I and II, while oncology had the lowest average probability of success in Phase III and ophthalmology had the lowest for registration to approval. Conversely, ophthalmology had the highest average probability of success in Phase I, hematology (56.6%) had the highest in Phase II, and musculoskeletal had the highest in Phase III and Registration to Approval. Psychiatry had the lowest overall likelihood of approval (LOA) at 6.7%, followed by oncology at 8.9%. Hematology (26.1%) had the highest overall probability of success, followed by infectious disease (21.6%), musculoskeletal (20.4%) and ophthalmology (20.4%).

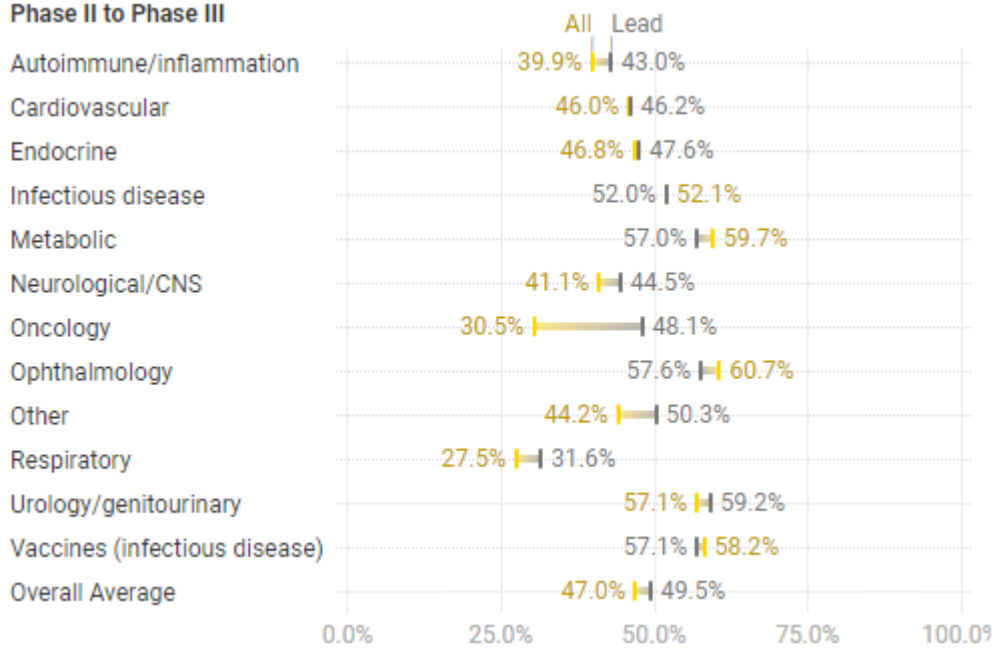
While the visual appearance of **Figure 4** seems to indicate that the Overall LOA should be higher than the 13% that was previously reported by **Figure 1**, the greater sample size for indications with lower overall LOAs, such as oncology, which can comprise as much as one-third of all pipeline products, decreases the LOA for all indications[10]. The lowest LOA in psychiatry (at 6.7%) comes from difficulty in establishing clinical advantage over the existing treatments especially in depression (e.g. Prozac and other selective serotonin reuptake inhibitors (SSRIs)), and with increased placebo response in placebo-controlled trials. The similarity in symptoms also often distracts from differing underlying pathologies, occasionally differing as well based on geographic regions, making it more difficult to treat the psychiatric disease in question.

Common perceptions often indicate that the oncology therapeutic area is the most difficult in terms of clinical trial success from Phase I to Approval, and, excluding psychiatry, that observation is true. Following a discussion of all and lead therapeutic areas, we will take a closer look at how oncological and non-oncological indications compare as well as differences between various oncological tumor types and indications.

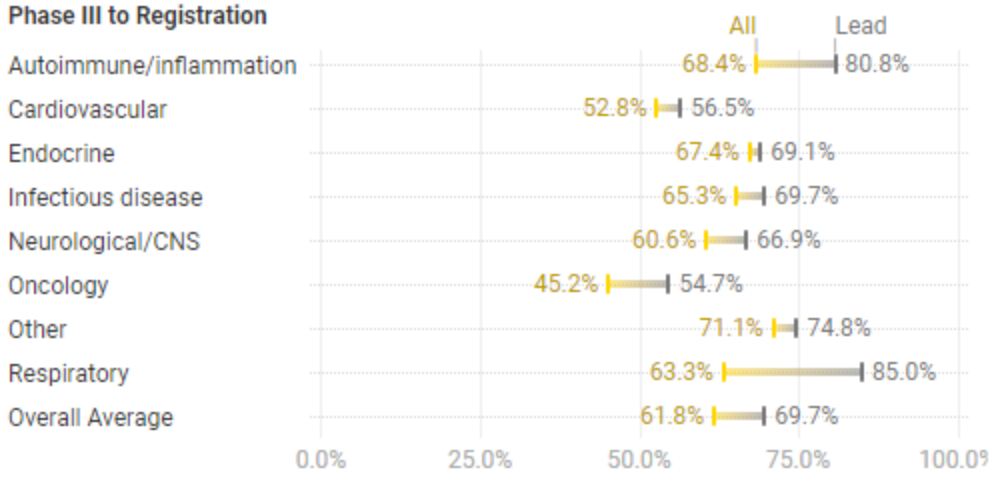
Figure 5 – Difference between All and Lead Indications



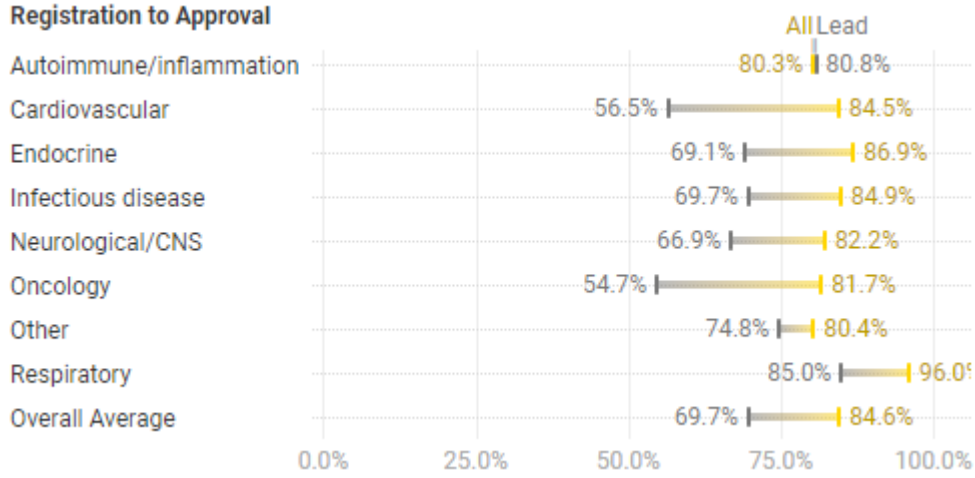
Phase II to Phase III



Phase III to Registration



Registration to Approval



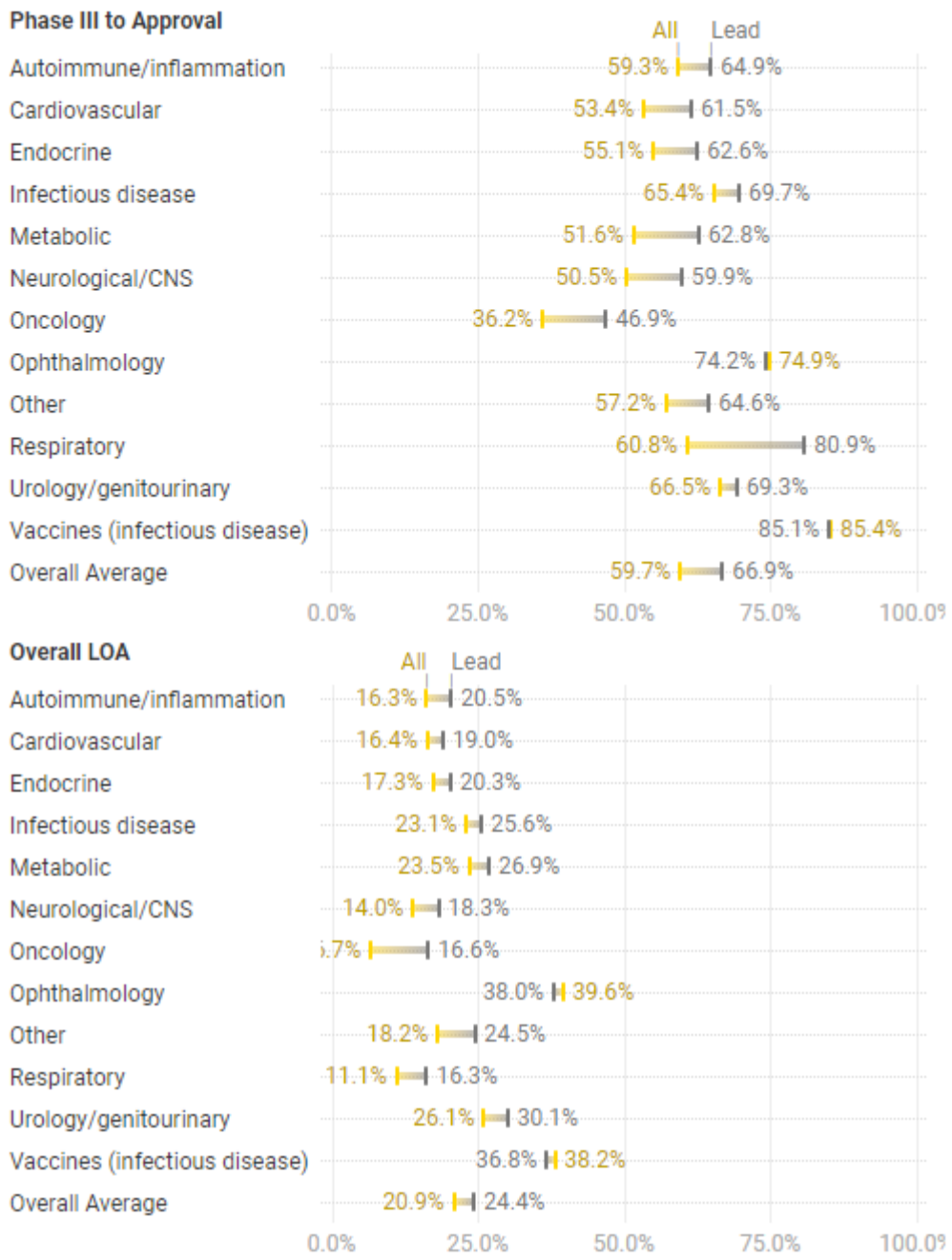


Figure 5. Comparison between All and Lead Therapeutic Areas
Data averaged from Wong et al (2018) and Hay et al (2014). Gray corresponds to lead indications while yellow corresponds to all indications. As Wong et al (2018) does not report separate values for Phase III to Registration and Registration to Approval, the Hay et al (2014) values for these stages are reported separately and the combined Phase III to Approval is reported afterward to incorporate Wong et al (2018).

Lead indications are defined by Wong et al (2018) as referring to the indication that is furthest in the drug development pipeline. If more than one indication is in the highest phase of development, the indication that reached that phase first is considered the lead indication. In this scenario, it is possible for the lead indication changes for a drug between phases as commercial priorities change. Lead indications are defined by Hay et al (2014) as the primary indication. An example given by Hay et al (2014) is that if an antibody is developed in four cancer indications and, at Phase III, three fail and one succeeds, the success rate for all indications is 25% while the success rate for the lead indication is 100%.

Across most indications and clinical phases, the lead indication generally performed better than all indications. Careful selection of the lead indications, especially early in

preclinical and clinical development, via scientific, monetary, or commercial prioritization may well be the cause of the higher overall LOA of lead indications compared to all indications.

The phase in which that differed was Registration to Approval, where all indications exceeded the probability of success of the lead indications. Based on Wong et al (2018) and Hay et al (2014)'s methodologies to determine a lead indication, it is highly likely that technical reasons, such as lack of efficacy, contributed to the cancellation or lack of approval of a lead indication following Phase III completion. Other cancellation reasons may include commercial or portfolio rationalization, perhaps due to a subsequent clinical trial for another indication that resulted in more promising data. Once the drug has already been approved, subsequent Phase II or Phase III trials, some of which occur concurrently with the initial Phase III and approval process, can enable a product to expand its label significantly. All these label expansions would have a higher probability of success at the approval stage, as the product has been previously reviewed and validated during the original regulatory review.

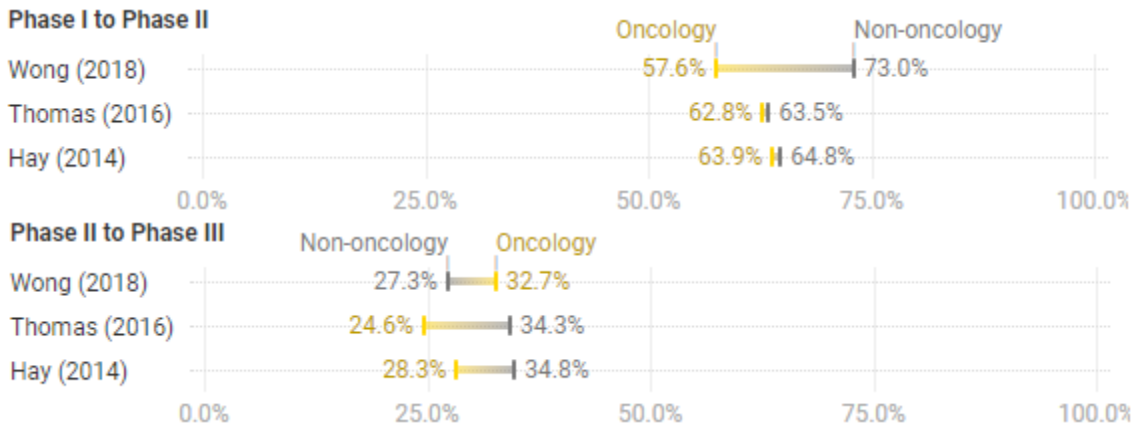
We will focus next on one of the most popular—and difficult—therapeutic areas, oncology, whose pipeline grew by 16% in 2016-17 and comprised nearly a third of the overall product pipeline[10].

Probability of Success by Oncological Indication

Oncology comprises one of the largest therapeutic classes and, as seen in **Figure 4**, has one of the lowest overall likelihoods of approval. Various breakdowns will enable us to gain more information about the differences between oncology and other therapeutic areas, oncological tumor types, and oncological indications.

First, we can compare oncological to non-oncological indications:

Figure 6 – Probability of Success for Oncological and Non-Oncological Indications



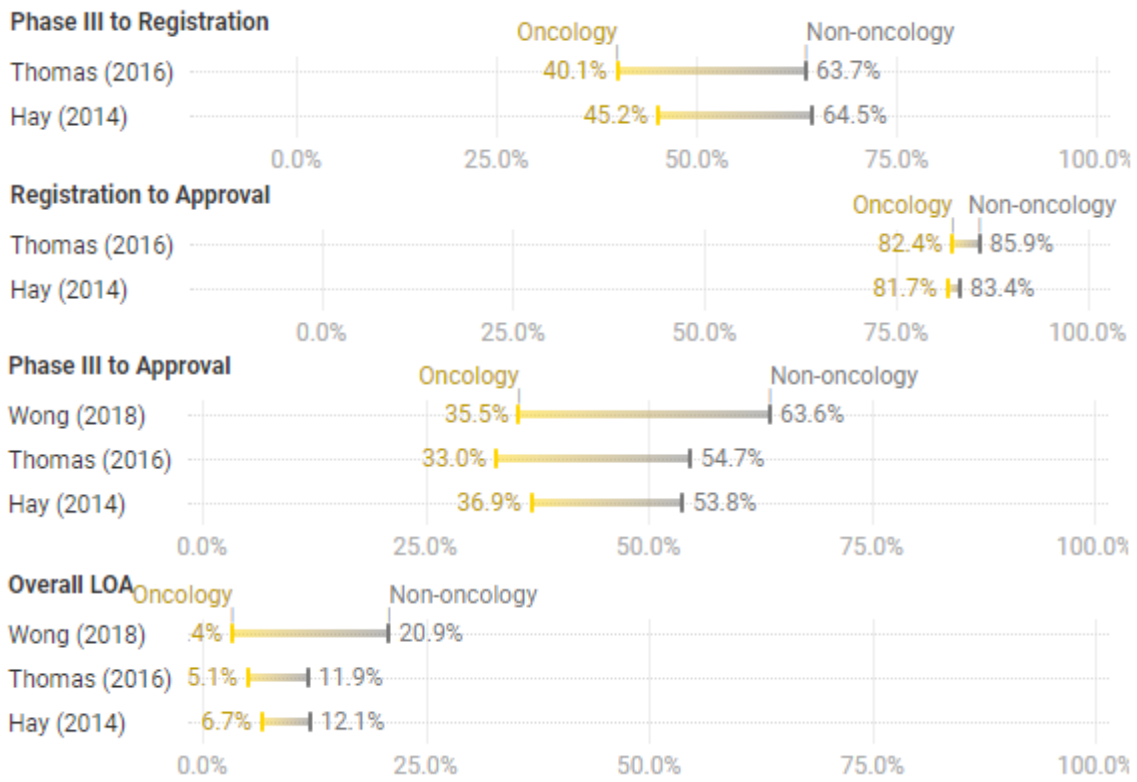


Figure 6. Comparison between Oncology and Non-oncology Indications
Data from Wong et al (2018), Thomas et al (2016), and Hay et al (2014) and compares oncological and non-oncological indications for the years 2003-2015. Yellow corresponds to oncology indications and gray corresponds to non-oncology indications. For all authors and phases of development (apart from Wong et al (2018) in Phase II to Phase III), non-oncology indications had a higher probability of success.

Non-oncological indications have a higher likelihood of success than oncological indications for all publications reviewed except for Phase II in Wong et al (2018). This difference is notable in Phase III, where non-oncological indications have a roughly 20% higher probability of success than oncological indications.

The difference may be due to, in part, the endpoint criteria chosen for oncology Phase III trials, possibility of severe side effects, and the frequent need to show at minimum non-inferiority or ideally superiority to an existing standard of care drug. These endpoints can include progression-free survival (PFS) or overall survival (OS), with the potential inclusion of radiological response rates. While surrogate markers enable a faster determination of efficacy and can occasionally lead to approval, the FDA often requires OS data for full approval, causing success in Phase II to not necessarily result in success in Phase III. OS data can be diluted with those patients that crossover from one treatment arm to another.

Another potential reason for the lower probabilities of success is the lack of a reliable non-human model for the pharmacokinetic properties and efficacy of compounds prior to initiating clinical development. The increased use of biomarkers for patient selection (as discussed in **Probability of Success by Biomarker Usage**) may help alleviate the

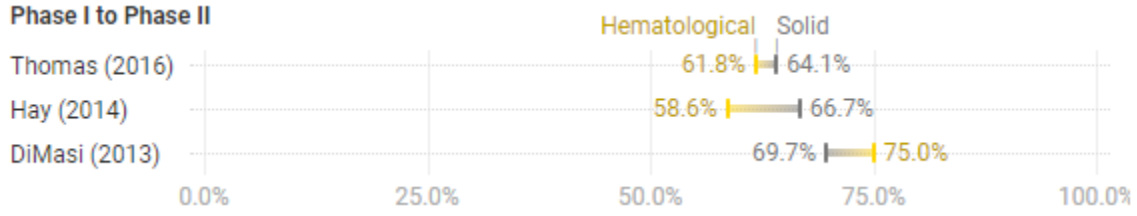
concerns in oncological development that drugs will not be efficacious or, worse, dangerous for a selected patient cohort.

Wong et al (2018) differed from both Thomas et al (2016) and Hay et al (2014) for Phases I and II, with a far greater difference between the publications in Phase I for Wong et al (2018) and a difference in trend between oncology and non-oncology in Phase II. The greater disparity seen in Phase I may come from the enrollment of cancer patients in oncology Phase I trials, unlike most other therapeutic areas that preferentially enroll healthy volunteers. The difference in methodology used by Wong et al (2018), detailed more extensively in **Appendix: Source Methodology**, also contribute to this difference, as it considers those indications that progressed directly from Phase I to Phase III as successes in Phase I and Phase II. As many oncological indications lack efficacious treatments or cause serious side effects, it is likely that more oncological drugs would receive fast track designations or accelerated approval compared to other indications. This would, in turn, result in more drugs moving past Phase II to proceed directly to Phase III, thereby increasing the probability of success for oncological Phase II drugs. Similarly, drugs that proceed from Phase II directly to registration would be considered as successes by Wong et al (2018) for both Phase II and Phase III.

This is not necessarily consistent with Hay et al (2014) and Thomas et al (2016), as these two sources both use a methodology that considers success in Phase x to be that the compound is now in Phase x+1. In this situation, a compound that skips a phase (goes to x+2) may be considered a failure, as it never actually reached x+1. This would result in decreases in the probabilities of success for the phases where such skipping is most likely. Another potential source of the differences between Wong et al (2018) and Hay et al (2014) and Thomas et al (2016) is the data source. While Wong et al (2018) includes non-industry clinical trials, both Hay et al (2014) and Thomas et al (2016) only include industry clinical trials.

Next, we can compare the probabilities of success of two primary tumor types, hematological and solid[11]:

Figure 7 – Probability of Success by Oncological Tumor Categories



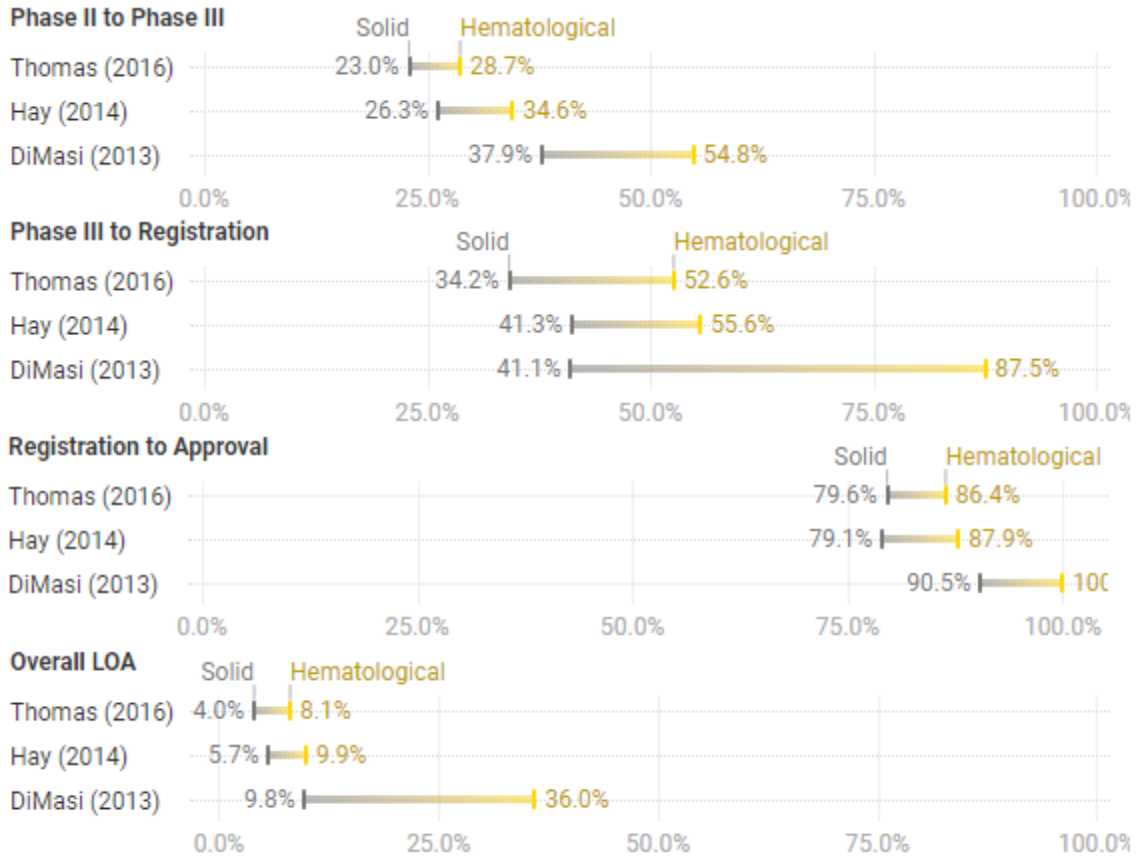


Figure 7. Comparison of Probability of Success between Hematological and Solid Cancers
Data from Thomas et al (2016), Hay et al (2014), and DiMasi et al (2013). Yellow corresponds to hematological tumors while gray corresponds to solid tumors. While solid tumors largely have a higher probability of success in Phase I, hematological cancers have a far higher probability of success starting in Phase II.

The switch from solid to hematological tumors following Phase I coincides with the switch from safety testing in Phase I to efficacy testing (Phase II and III). A large concern for hematological cancers is safety, which is seen in its lower probability of success for Phase I. Conversely, penetration into the tumor, toxicity, and mechanistic insufficiency are primary concerns for solid tumors, restricting their probability of success in Phase II and III.

DiMasi et al (2013), which focused exclusively on oncology probability of success, calculated very different solid and hematological probabilities of success across the clinical development pipeline as compared to Thomas et al (2016) and Hay et al (2014). This can be attributed to the years the publication evaluated—1993 to 2004—which has very little overlap with the periods evaluated by Thomas et al (2016)—2006-2015—and Hay et al (2014)—2003-2011. The limited sample sizes for the period evaluated by DiMasi et al (2013)—625 total compounds with only 50 hematological cancer-only compounds—also contributed to the differences seen between the sources.

The difference between the tumor types can be further explored by breaking down each category into its constituent indications:

Figure 8 – Probability of Success by Oncological Indication

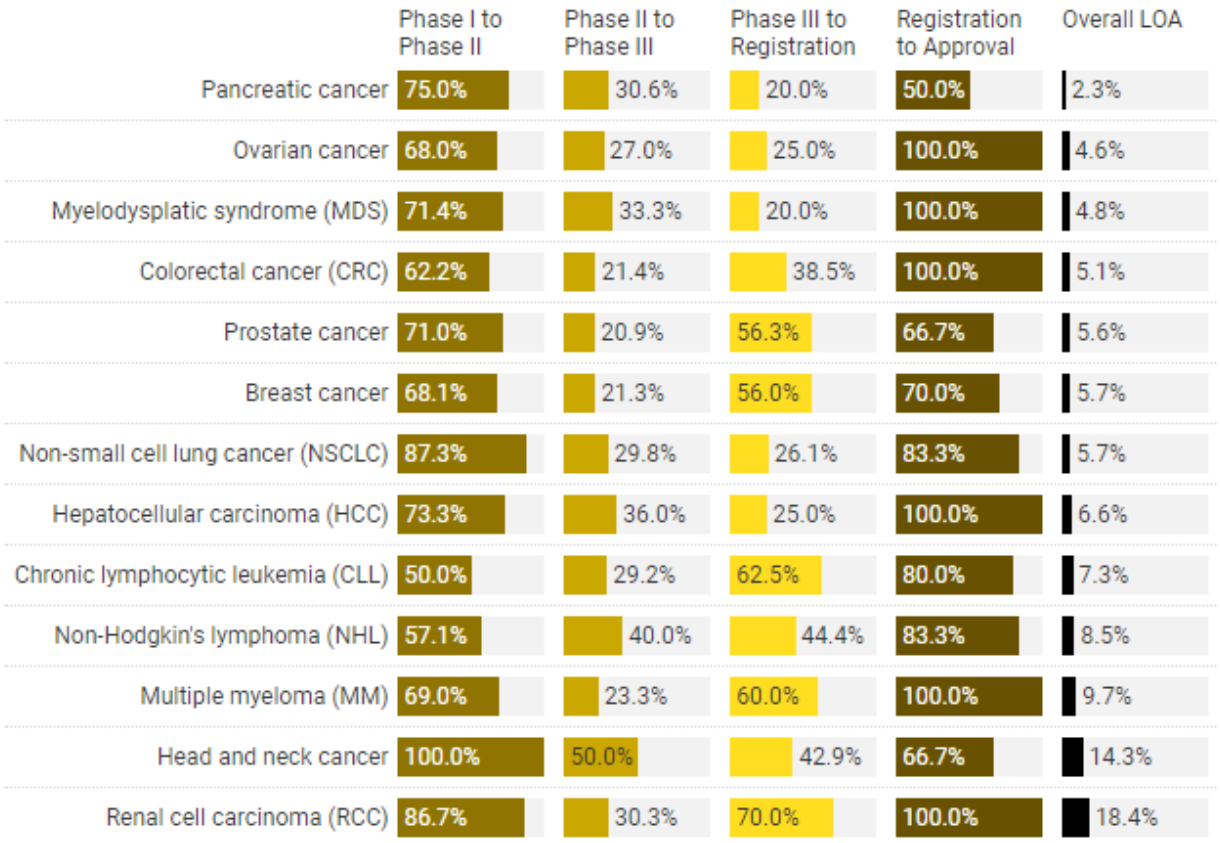


Figure 8.Comparison of Probability of Success of Various Oncological Indications
Data from Hay et al (2014). It is important to note that the sample size for several of the indications is very small, which may result in misinterpretation of the values provided. For example, Hay et al reported a 100% NDA/BLA to approval phase success on a sample of 1 for hepatocellular carcinoma (HCC) and ovarian cancer.

The highest probabilities of success in Phase I were seen in head and neck cancer (n=5, 100%), non-small cell lung cancer (n=55, 87.3%), and renal cell cancer (n=15, 85.7%) while chronic lymphocytic leukemia had the lowest probability of success at 50% (n=12). The Phase II probability of success of head and neck cancer is far higher (n=12, 50%) than the two lowest, breast cancer (n=61, 21.3%) and colorectal cancer (n=56, 21.4%). Phase III probability of success values varied widely between indications, from 20% for pancreatic (n=10) and myelodysplastic syndrome (n=5) to 62.5% for chronic lymphocytic leukemia (n=8) and 70% for renal cell carcinoma (n=10). For NDA/BLA to approval, of the indications with 100% approval, renal cell carcinoma (n=6), colorectal cancer (n=4), multiple myeloma (n=4), and myelodysplastic syndrome (n=3) have sample sizes larger than 1.

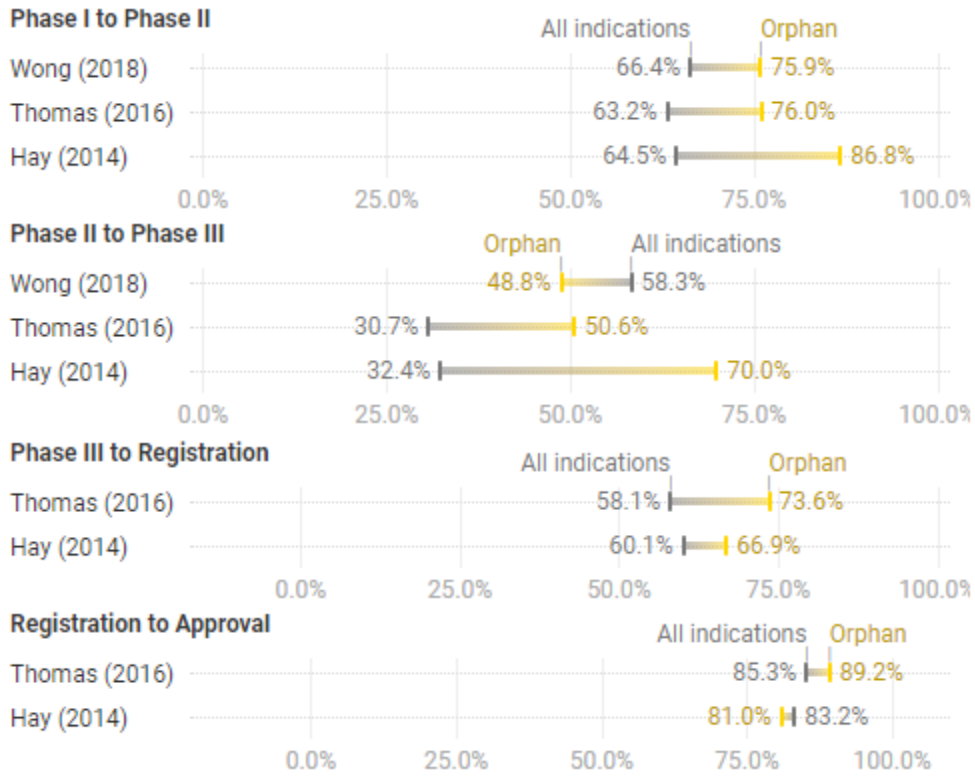
Despite earlier trials attempting to de-risk the larger and costlier Phase III trials, most oncology drugs that fail Phase III trials fail due to efficacy or safety concerns[12]. Subsequent failures at regulatory approval are likely due to the failure to meet the primary endpoint despite the success of secondary endpoints, in addition to insufficient data in the initial approval process. To avoid such costly Phase III failures, particularly in a therapeutic area of such high clinical need, drug makers should consider biomarker inclusion for and optimization of patient selection, better internal review of endpoints, and use of an adaptive design.

One area in which success in Phase II and III is particularly low is pancreatic cancer. It is the fourth leading cause of cancer death in the US, partially due to its late diagnosis stage, elderly affected population, and tendency to metastasize early[13], and compounds in the clinical development pipeline have historically been granted Orphan Drug Designations, as BERG received in January 2018 for BPM31510 (ubidecarenone)[14]. The low probability of success in clinic has been linked to the tendency to move into Phase III trials following promising secondary endpoint or subset data in Phase II trials, without consideration of the primary endpoint[15]. Of the 39 Phase III trials in advanced pancreatic cancer from 1997 to 2015, 85% of these started prior to the Phase II trial meeting its primary endpoint[15].

Probability of Success by Orphan/Rare Disease Designation

The FDA Orphan Drug Designation program applies to the compounds intended for rare diseases or disorders that "affect fewer than 200,000 people in the U.S." or affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug"[16]. These drugs frequently benefit from accelerated drug development pathways, often allowing to complete either Phase II or Phase III studies, rather than both as required for most other drugs:

Figure 9 – Probability of Success by Orphan Designation



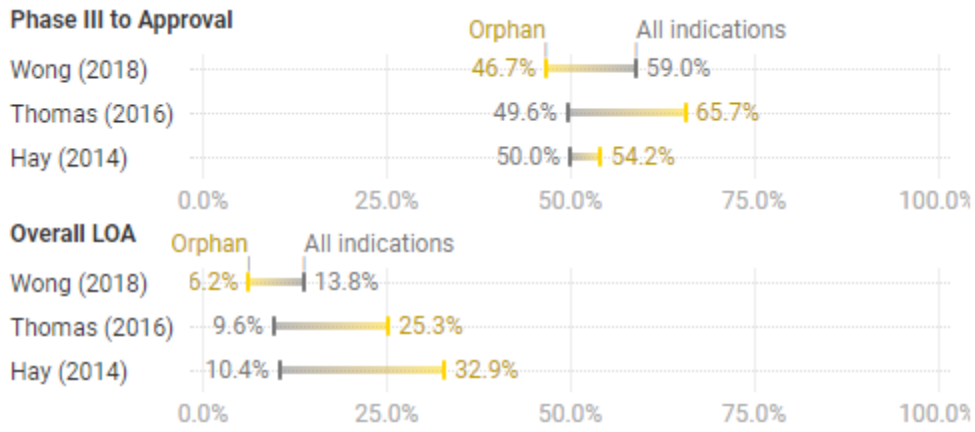


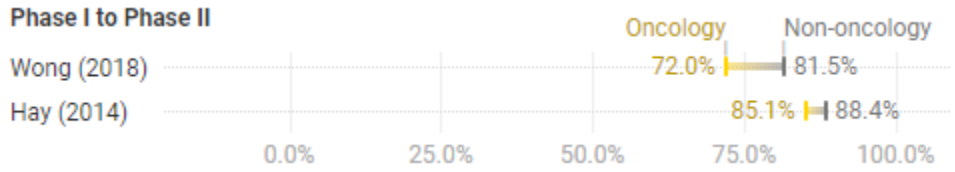
Figure 9. Comparison between Orphan Indications and All Other Indications
Data from Wong et al (2018), Thomas et al (2016), and Hay et al (2014). Yellow corresponds to orphan indications while gray corresponds to all indications. Orphan indications had a higher probability of success for Phase I and for Thomas et al (2016) and Hay et al (2014) until Approval. Wong et al (2018) showed that all indications had a lower probability of success than all indications following Phase I success.

Orphan indications overall had a higher probability of success than All Indications for Thomas et al (2016) and Hay et al (2014), which would be expected based on the truncated clinical development paths orphan drugs typically experience. Of 99 trials for 67 indications evaluated by Gaddipati et al (2012)[17], only 25 indications (37% of the data set) were approved based on the results of more than one trial.

However, Wong et al (2018) showed that orphan indications performed worse than All Indications. While the differences between Wong et al (2018) and Thomas et al (2016) can be explained by Thomas et al (2016)'s exclusion of oncology rare diseases from their calculation, the same does not hold true for Hay et al (2014). The Phase II probability of success in Hay et al (2014) may be inflated based on when orphan designations for drugs in their data set were received. Of the 170 orphan drugs evaluated by Hay et al (2014), 82% received their orphan designation prior to Phase III and during Phase I (22%) or II (45%).

Evaluating the difference between oncological and non-oncological rare or orphan diseases provides insight into why Wong et al (2018) had a lower probability of success for Phases II and III for orphan drugs (**Figure 9**), as oncology comprised 60% of 2084 drugs for orphan indications evaluated by Wong et al (2018) and 50% of a far smaller data set of 170 for Hay et al (2014):

Figure 10 – Probability of Success for Oncology and Non-Oncology Orphan Indications



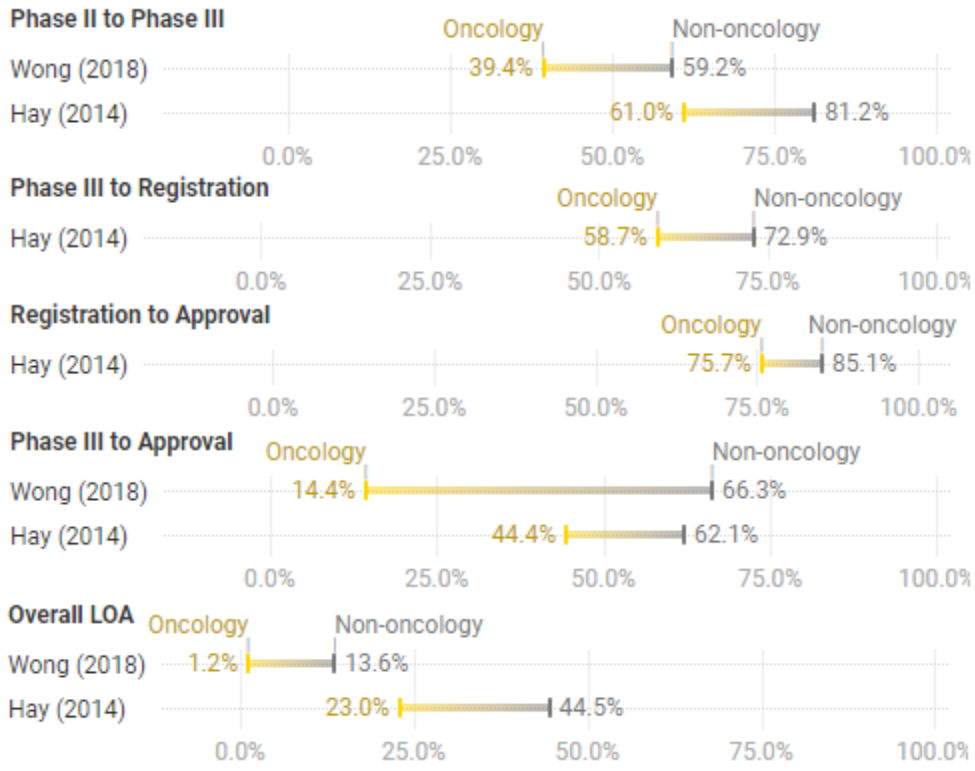


Figure 10. Comparison of Probability of Success for Oncological and Non-Oncological Indications
Data from Wong et al (2018) and Hay et al (2014). Yellow corresponds to oncological indications while gray corresponds to non-oncological indications. While Thomas et al (2016) only includes non-oncology indications as rare diseases (and was therefore removed from this evaluation), both Hay et al (2014) and Wong et al (2018) include oncological indications in their primary calculation of orphan drug success rates.

As in **Figure 6**, oncological indications had lower probabilities of success than non-oncological indications. While many orphan indications (and oncological orphan indications) only require either a Phase II or III trial rather than both because of the limited number of potential patients, that does not equate to success in either trial. Difficulties in selecting suitable endpoints and patients are especially pronounced in orphan oncology indications, where the standard of care may be a chemotherapy regimen and the patients may have undergone previous lines of therapy. Overall response rate, rather than overall survival, or surrogate endpoints are often used due to the high use of nonrandomized, unblinded—and occasionally single-arm—trials to accommodate the limited number of eligible patients[17].

The difference between oncological indications and non-oncological indications is more pronounced when broken down by individual orphan therapeutic area:

Figure 11 – Probability of Success by Orphan Indication

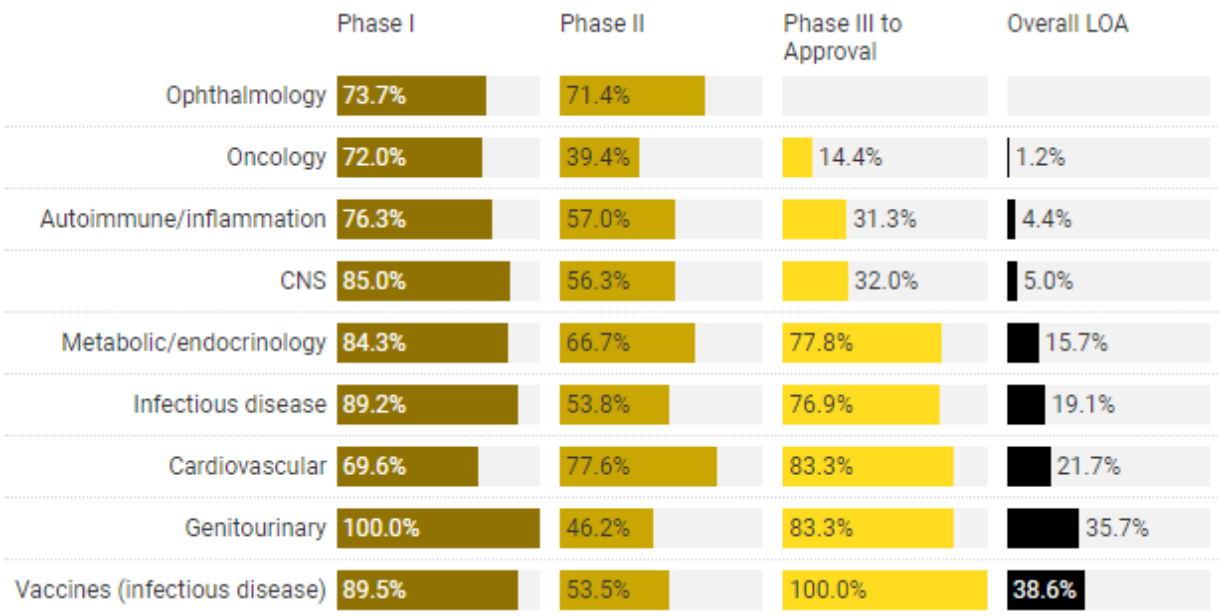


Figure 11. Comparison of Probability of Success across Orphan Indications
Data from Wong et al (2018). Ophthalmology had no paths from Phase III to approval in the data set reviewed by Wong et al (2018), resulting in no Overall Likelihood of Approval (LOA) value. The vaccines category is specific for infectious disease. CNS is an abbreviation for central nervous system. Ophthalmology had an n=19 in Phase I to II, n=7 in Phase II to III, and n=0 paths for Phase III to Approval, hence the lack of an Overall LOA value.

Among the orphan indications, oncology and CNS/neurology have been specifically associated with a higher risk of serious adverse events relative to non-orphan drugs in the same therapeutic class[18]. With orphan diseases, a particularly difficult aspect is the limited patient pool for clinical trials, many of whom may have been previously treated with other drugs and therefore may be ineligible for the trial. The lack of understanding for many of the mechanisms behind orphan diseases may well be the cause of the far lower oncology, autoimmune/inflammation, and CNS probabilities of success, particularly after Phase III, when surrogate endpoints and unblinded (or unrandomized) studies are far more common.

With the advances in biomarker usage for patient selection and as surrogate endpoints for clinical trials, we need to evaluate the effects that biomarker usage has on clinical trial success.

Probability of Success by Biomarker Usage

A biomarker trial for both **Figure 12** and **Figure 13** is defined as a study that uses biomarkers for patient selection.

As Wong et al (2018) note, only 7.1% of all development paths including biomarkers use them for all phases of development, with Thomas et al (2016) reporting that 5% of the 9,985 phase transitions reviewed used biomarkers for patient stratification. Biomarkers are most often used for oncology, with 10,485 of the total 21,255 phase transitions reported by Wong et al (2018):

Figure 12 – Probability of Success by Biomarker Usage for Patient Selection

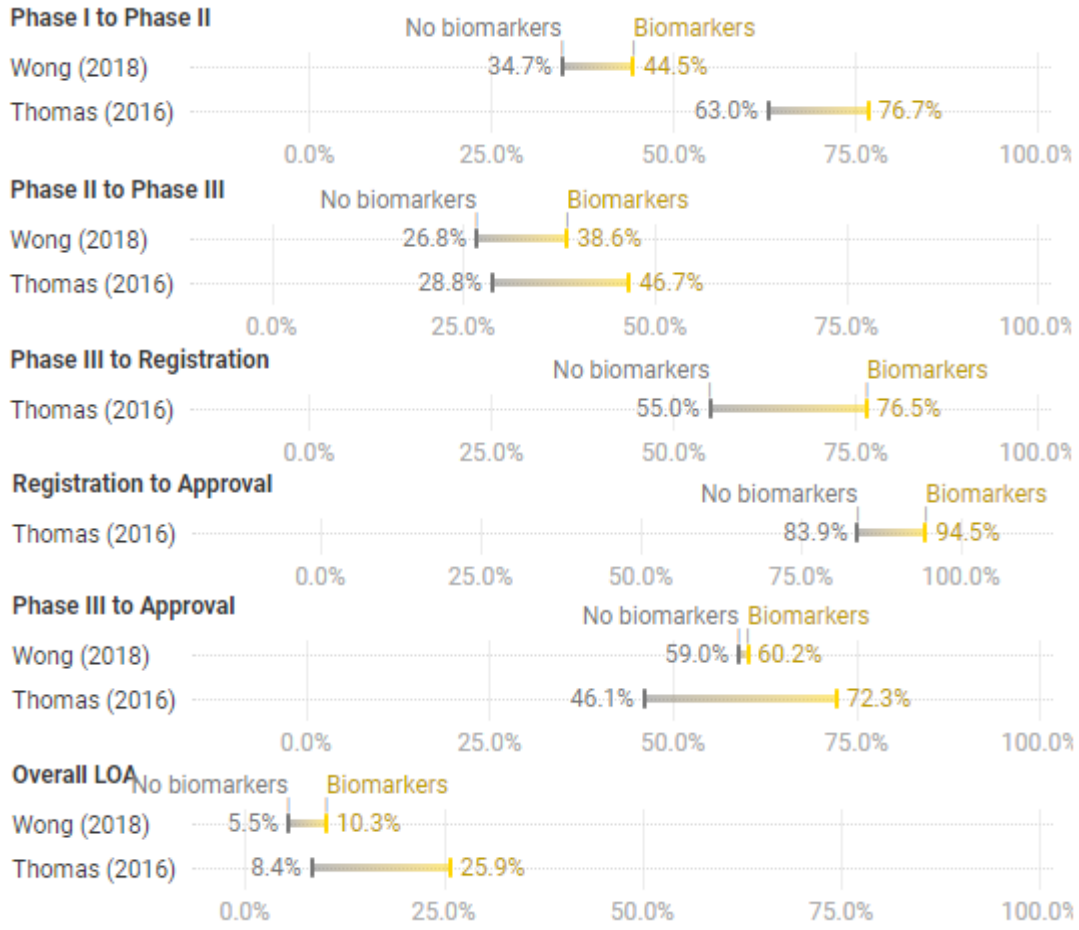


Figure 12. Comparison of Probability of Success based on Biomarker Usage for Patient Selection
Data from Wong et al (2018) and Thomas et al (2016). Yellow corresponds to biomarkers and gray corresponds to no biomarkers for patient selection. For all phases of clinical development and for both publications, biomarkers for patient selection resulted in an increase in the probability of success. The overall likelihood of approval nearly doubled for biomarker usage from 5.5% to 10.3% for Wong et al (2018) and more than tripled from 8.4% to 25.9% for Thomas et al (2016) for all indications.

The ability to select those patients for whom the drug would be most suitable should improve the drug's success, and, as expected, biomarker usage for patient selection for clinical trials greatly improved the probability of success. The inclusion of biomarker usage data in the regulatory approval process likely provided an additional surrogate endpoint for the pivotal trial and improved the case for approval, thereby increasing the probability of success at this stage.

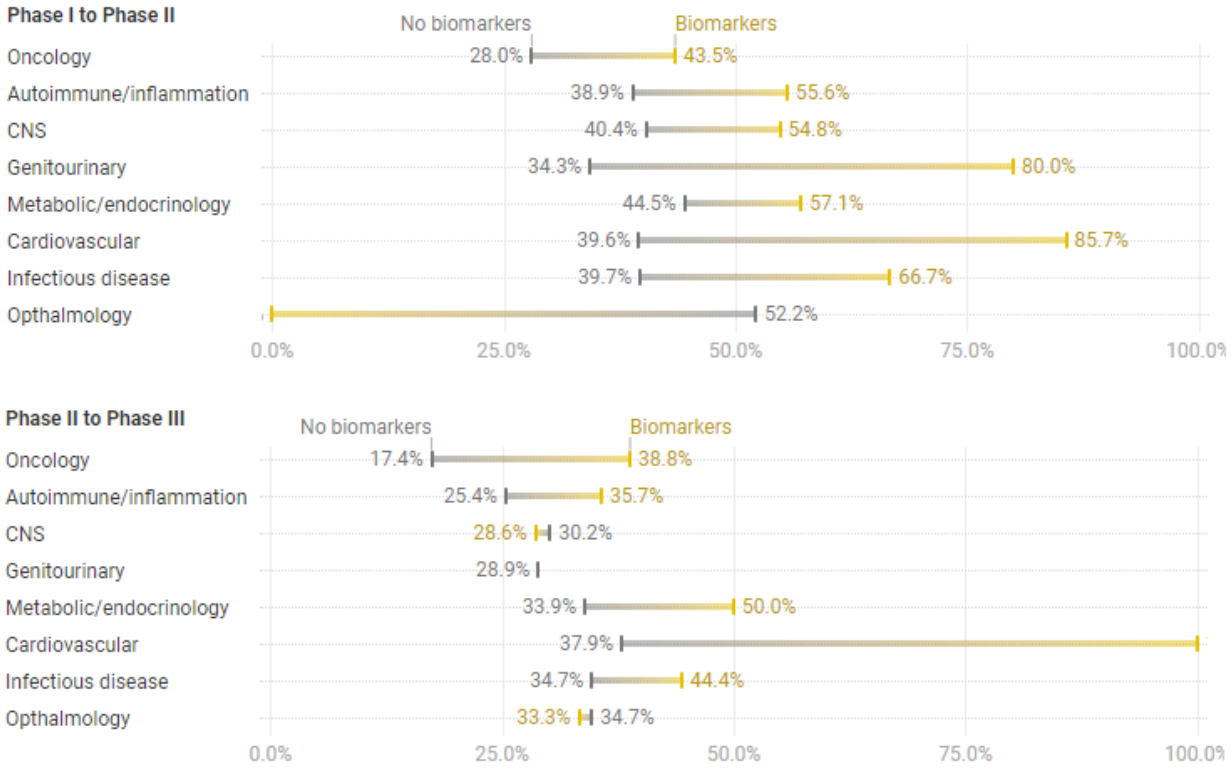
However, the two sources differed on the probability of success in Phase I for both biomarker usage and no biomarker usage as well as how much of a positive effect biomarker usage for patient stratification had on the probability of success from Phase III to Approval. In Wong et al (2018), over half of the clinical trials for Phase I to II for both biomarker usage and no biomarker usage were identified as coming from oncology, which has one of the lowest probabilities of success of all indications.

Thomas et al (2016) does not specify the source of its 42 trials with selection biomarkers and the 3480 without at Phase I to Phase II. This may therefore be the difference for Phase I to Phase II between the two publications.

Other potential sources of differences include: a) different sources used by the respective publication, as Wong et al (2018) used Trialtrove and Pharmaprojects while Thomas et al (2016) used BioMedTracker, and b) different periods evaluated by the publications, as Wong et al (2018) covered 2000-2015 and Thomas et al (2016) examined 2006-2015.

Indication-specific evaluation of biomarker usage for patient selection can provide a better view of the importance of biomarker usage and validation:

Figure 13 – Biomarkers for Patient Selection Probability of Success by Indication



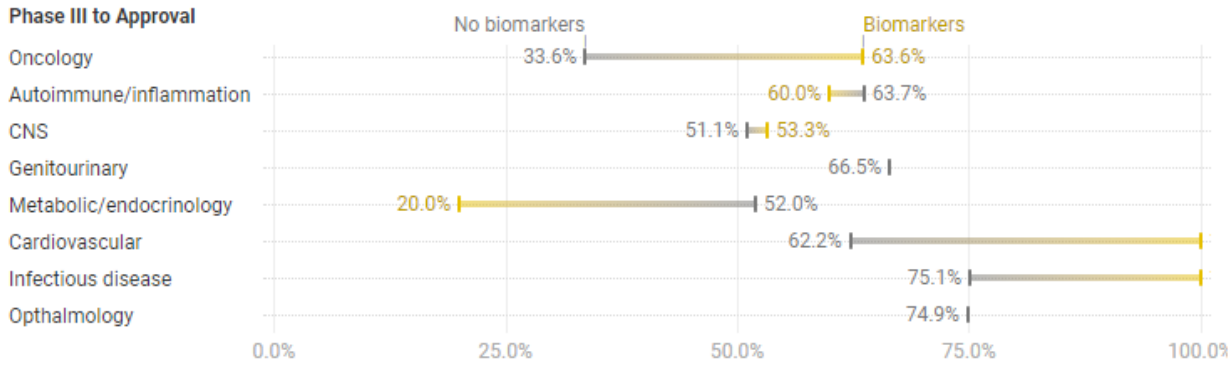


Figure 13. Comparison by Indication of Probability of Success based on Biomarker Usage for Patient Selection
Data from Wong et al (2018). Yellow corresponds to biomarkers and gray corresponds to no biomarkers. Ophthalmology's 0% value in Phase I to Phase II comes from the failure of the sole trial that incorporated biomarkers for patient selection at that phase. Genitourinary and vaccines for infectious disease were excluded, as they had N/A for more than one stage of clinical development.

The large disparities seen with the metabolic/endocrinology and the cardiovascular indications come from the limited sample sizes for biomarker trials outside of oncology, which comprises more than half of all studies that use biomarkers for patient selection. A better understanding of the exact role that biomarkers play in improving clinical probability of success will be become clearer as more studies outside of oncology begin to incorporate them.

Similar trends of are not consistently seen, however, when the definition for biomarker usage is expanded to include trials with the "objective of evaluating or identifying the use of any novel biomarker as an indicator of therapeutic efficacy or toxicity", as described by Wong et al (2018):

Figure 14 – Overall Biomarker Usage Probability of Success

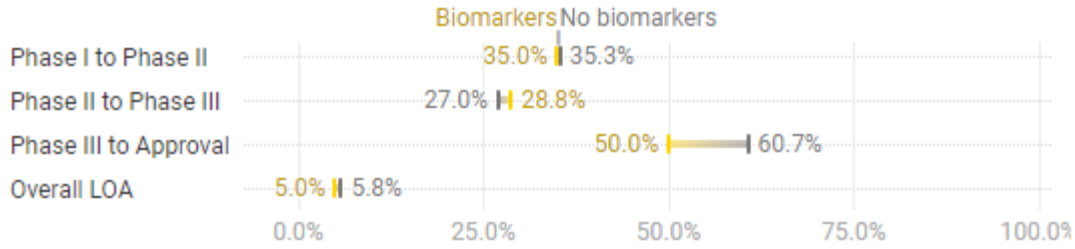


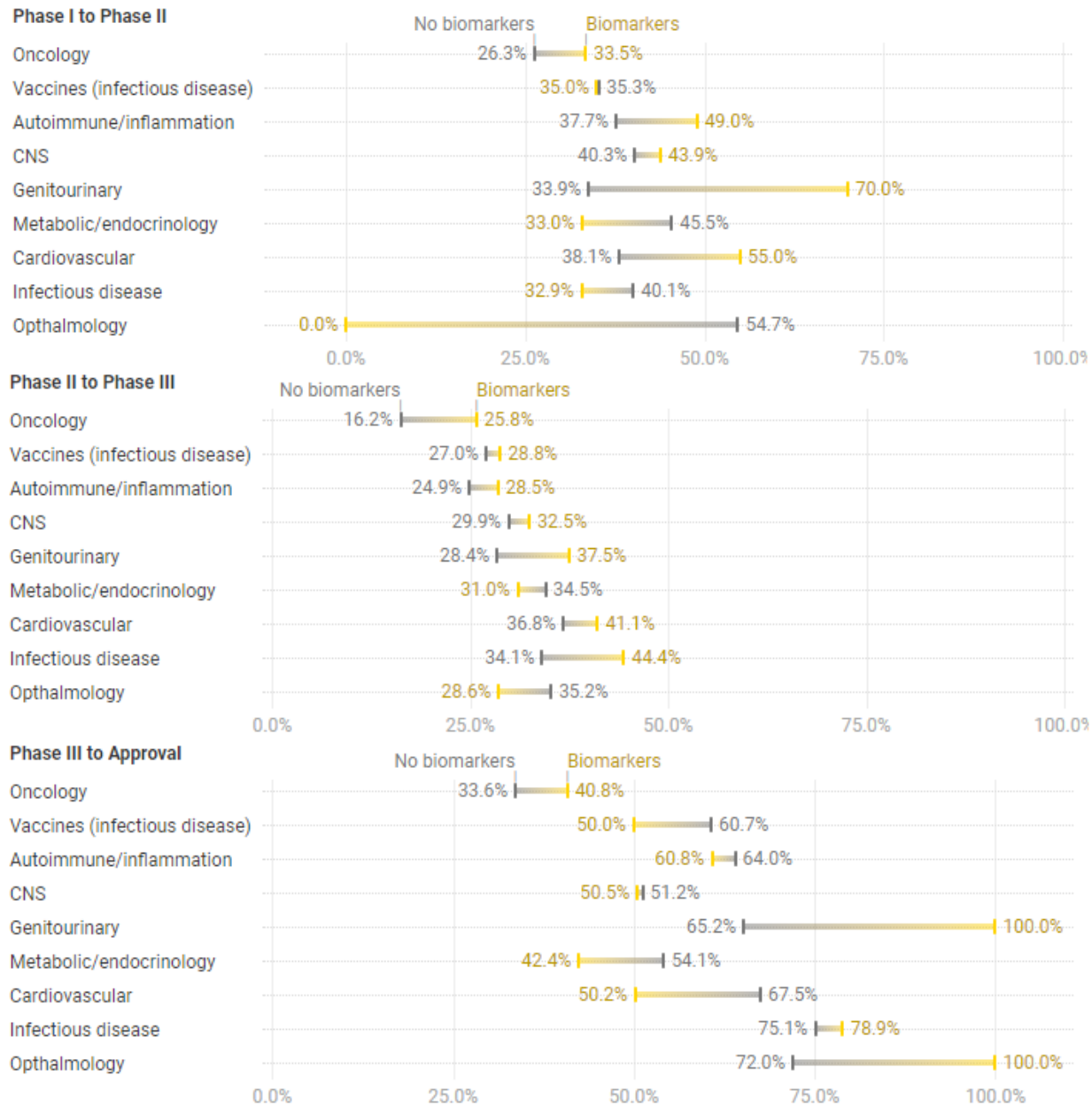
Figure 14. Comparison of Probability of Success based on Biomarker Usage for Patient Selection, Biomarker Identification, and Biomarker Evaluation
Data from Wong et al (2018) and compares biomarker usage for patient selection and stratification and biomarker evaluation and identification for the years 2005 to 2015. Yellow corresponds to biomarkers and gray corresponds to no biomarkers. LOA is an abbreviation for likelihood of approval.

When the definition was expanded, the biomarker usage had a slightly overall negative effect on LOA due to the decrease in Phase III to Approval. This decrease in Phase III to Approval is likely attributed to those trials attempting and failing to investigate or validate the role of a potential biomarker in a disease in a Phase III trial. This does not

discount the possibility of regulatory failure following Phase III success, perhaps due to lack of evidence of the biomarker's role in validating a surrogate endpoint.

When looking at the breakdown by indication (**Figure 15**), biomarker usage does not result in a significant increase in the probability of success, with only genitourinary indications experiencing a large increase in overall probability of success:

Figure 15 – Overall Biomarker Usage Probability of Success by Indication



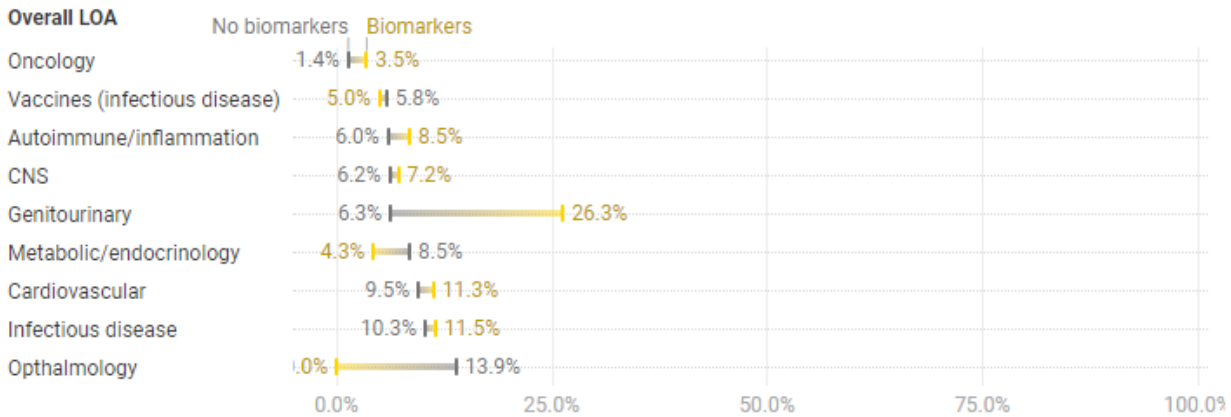


Figure 15. Comparison of Probability of Success by Biomarker Usage for Patient Selection, Biomarker Identification, and Biomarker Evaluation *Data from the Supplementary Material for Wong et al (2018) and compares biomarker usage for both patient selection and biomarker evaluation/identification for the years 2005 to 2015. Yellow corresponds to biomarkers and gray corresponds to no biomarkers.*

Sample sizes differed between therapeutic areas when biomarkers were used for both patient selection and biomarker evaluation or identification. The oncology indications had as many as 4,986 reported phase transitions for Phase I to Phase II. For genitourinary, ophthalmology, and vaccines for infectious disease, the sample sizes for each stage were limited for biomarker usage, up to n=21: for genitourinary, the sample sizes were n=10 for Phase I to II, n=16 for Phase II to III, and n=8 for Phase III to Approval; for ophthalmology, sample sizes were n=9 for Phase I to II, n=21 for Phase II to Phase III, and n=21 for Phase III to Approval; for vaccines for infectious disease, n=15 for Phase I to II, n=18 for Phase II to Phase III, and n=12 for Phase III to Approval.

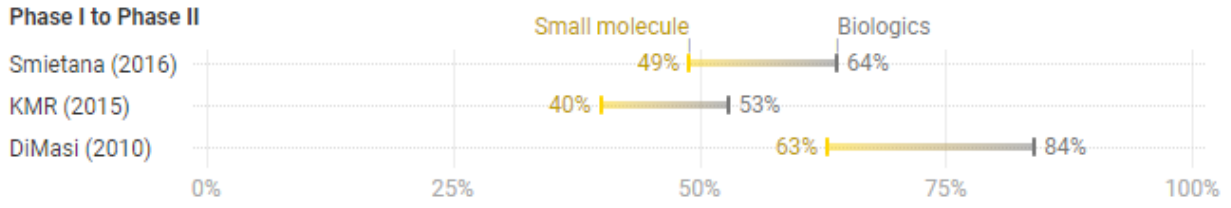
The inconsistent effect of biomarker usage for patient selection, biomarker identification, or biomarker evaluation is likely attributed to an increased failure rate of trials seeking to identify or evaluate the effectiveness of biomarkers. The limited sample sizes in several of the indications contribute to the 100% probabilities of success in Phase III to Approval for genitourinary and ophthalmology indications.

The previous sections of this report have included all drug classes for each indication and therapeutic class, but it is important to evaluate, as new modalities arise, the probability of success of a compound by drug class.

Success Rates by Drug Class

The first comparison can be made between small molecules and biologics (**Error! Reference source not found.**). Consistently for all phases apart from registration to approval, the biologics have a higher probability of success than small molecules; only KMR data for registration to approval disagrees, with a 4% decrease from biologics to small molecules[19]:

Figure 16 – Probability of Success for Small Molecules and Biologics



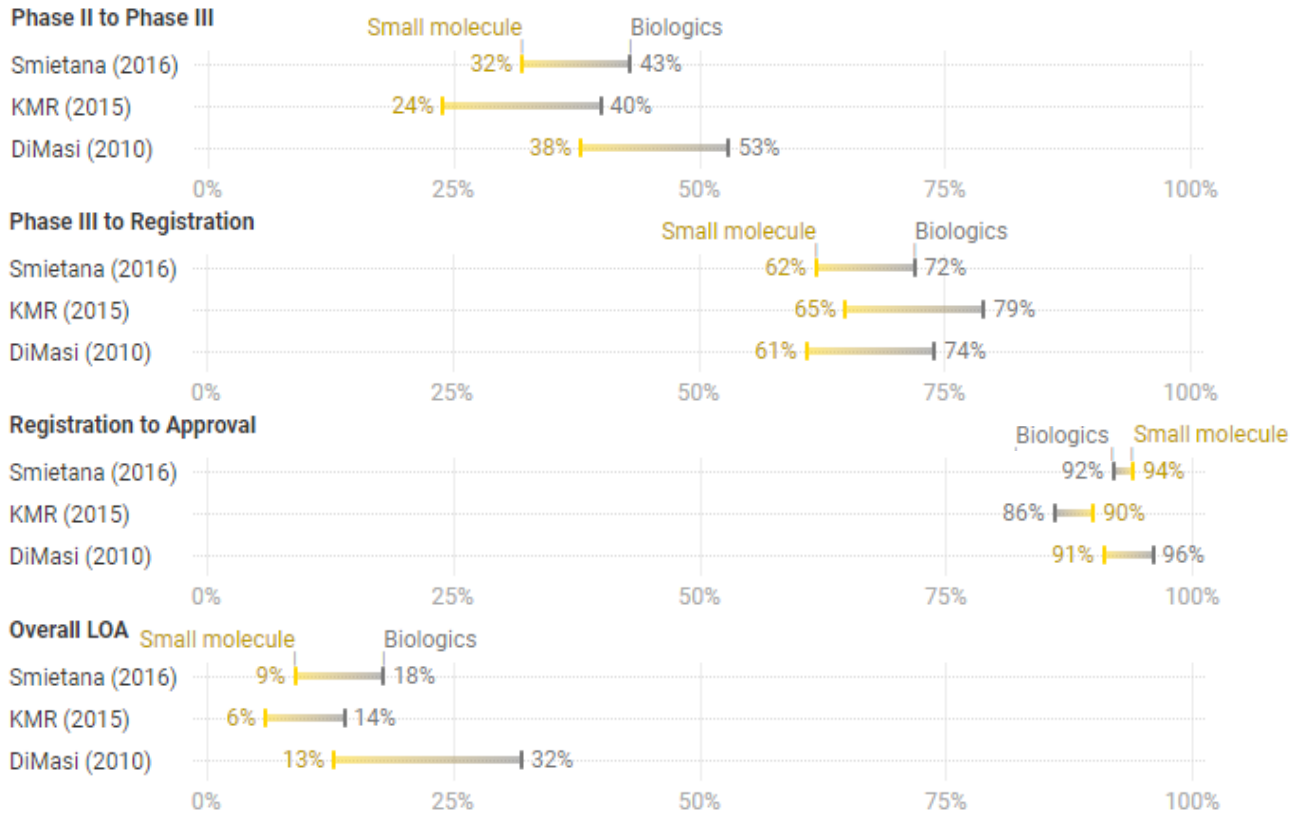


Figure 16. Comparison of Probability of Success for Biologics and Small Molecules
Data from Smietana et al (2016), KMR (2015), Hay et al (2014), and DiMasi et al (2010). Yellow corresponds to small molecules and gray corresponds to biologics.

Biologics have an overall high probability of success across all clinical phases due to the higher likelihood that a biologic is a targeted therapy and has undergone further validation during preclinical studies. Smietana et al (2016) and KMR (2015) showed a decrease in Registration to Approval with biologics while DiMasi et al (2010) showed an increase. The source and years for the data may be the reason for the difference, as the KMR (2015) data came from major pharmaceutical companies from 2010 to 2014 and Smietana et al (2016) compiled data from 1996 to 2014, while DiMasi et al (2010) reported data from 1993 to 2004. More recent clinical studies are more likely to involve surrogate endpoints, particularly in oncology, as only 36% of oncology clinical trials between 2005 and 2009 contained overall survival as a primary endpoint, a drop from 49% between 1995 to 2004 (within the period covered by DiMasi et al)[20].

These broad categories can be further subdivided into the drug classes as defined by the FDA, which include new molecular entities (NMEs), biologics, non-NMEs, and vaccines:

Figure 17 – Probability of Success by FDA Drug Class

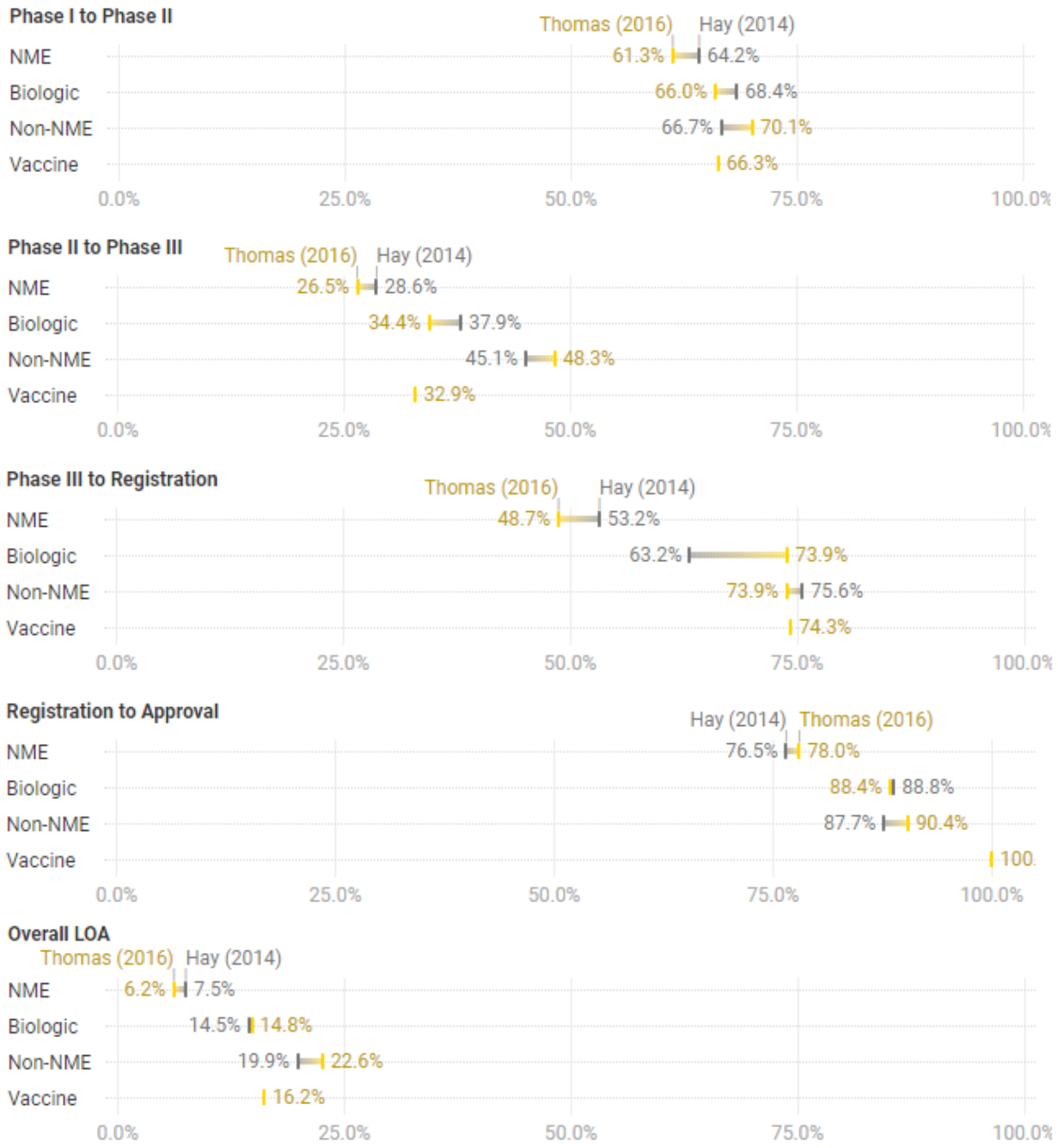


Figure 17. Comparison of Probability of Success by FDA Drug Class
Data from Thomas et al (2016) and Hay et al (2014). Yellow corresponds to small Thomas et al (2016) and gray corresponds to Hay et al (2014). LOA is an abbreviation for likelihood of approval. Only Thomas et al (2016) contained information about the vaccine probability of success, as defined by the FDA.

New molecular entity (NME) is not defined in any status or regulations but is defined by the FDA for a Type 1 NDA as an "active ingredient that contains no active moiety that had been previously approved" by the FDA whether in an "application submitted under section 505 of the Act" or "has been previously marketed as a drug in the United States"[21]. If the drug product contains a previously approved or marketed active moiety but the specific "ester, salt, or noncovalent derivative" has not been approved or marketed within the United States, the drug is not classified as an NME. It is therefore possible for the category of NMEs to include large molecules (such as biologics) and for non-NMEs to include small molecules. 13% of the drugs presented by Hay et al (2014) and considered NMEs by the FDA are large molecules. Of the FDA drug classes, NMEs had the lowest probability of success through the drug development stages, with an overall likelihood of approval of 6.2% (Thomas) and 7.5% (Hay), followed by biologics at 14.8% (Thomas) and 14.5% (Hay).

While the two publications had some differences, the overall trends were similar with NMEs having the lowest overall probability of success. These differences can be attributed to the difference in years evaluated by each publication, as Thomas et al (2016) reviewed data from 2006 to 2015 and Hay et al (2014) reviewed data from 2003 to 2011, and both publications used BioMedTracker as their source of data. For more recent results, Thomas et al (2016) would be the more reliable resource.

As NMEs are new, unapproved moieties, the lower probabilities of success in Phase II and Phase III are expected, particularly in Phase III due to the large efficacy-focused clinical trials that take place. Many non-NMEs, as noted by both Thomas et al (2016) and Hay et al (2014) due to several shared authors, begin development at Phase II or Phase III, and are often testing new formulations or combinations with understood and approved drugs. This decreases their risk associated with the clinical trial and contributes to their higher overall LOA.

These drug classes can be further broken down into small molecule NME, monoclonal antibodies (mAbs), non-mAb proteins, vaccines, and other large molecules (such as cytokines, but excluding steroids):

Figure 18 – Probability of Success by Drug Class

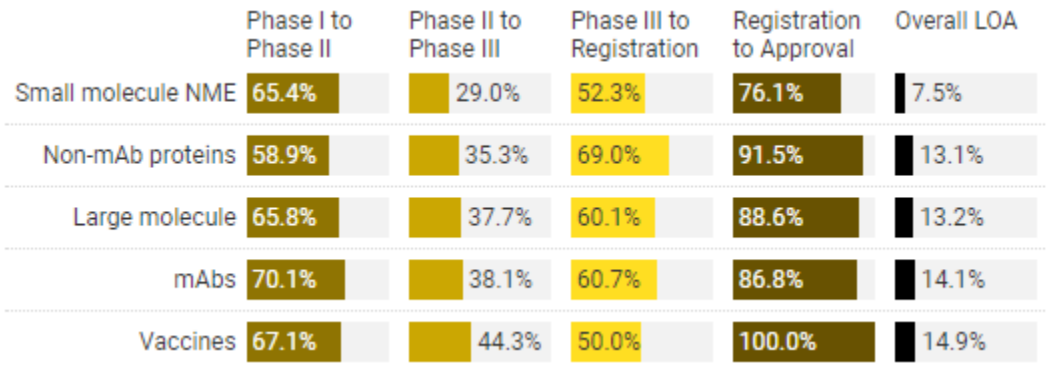


Figure 18. Comparison of Probability of Success by Drug Class
Data from Hay et al (2014) and compares different drug classes for the years 2003-2011. Small molecule NMEs had the lowest overall likelihood of approval (LOA) due to the lower probability of success starting in Phase II to Approval. NME is an abbreviation for new molecular entity. mAb is an abbreviation for monoclonal antibody. LOA is an abbreviation for likelihood of approval.

All 20 vaccines evaluated in Registration to Approval were successful, greatly increasing the drug class' probability of success.

As before, small molecule NMEs had the lowest overall likelihood of approval, as a result both of potential increased screening during preclinical studies and the higher likelihood of targeted large molecule and biologic therapies. Vaccines, surprisingly, had the highest overall likelihood of success, owing to the 100% success in the Registration to Approval phase. However, the Phase III to Registration probability of success for vaccines was lowest, because of the inclusion of cancer vaccines and other vaccines in addition to the infectious disease vaccines that had been previously evaluated by other publications as a separate therapeutic area.

To verify the role that cancer vaccines had on the decrease in the probability of success for vaccines and to understand the role of oncology drugs on the probabilities of success of various drug classes, an examination of oncology versus non-oncology drugs can be performed:

Figure 19 – Probability of Success for Oncology vs Non-Oncology by Drug Class

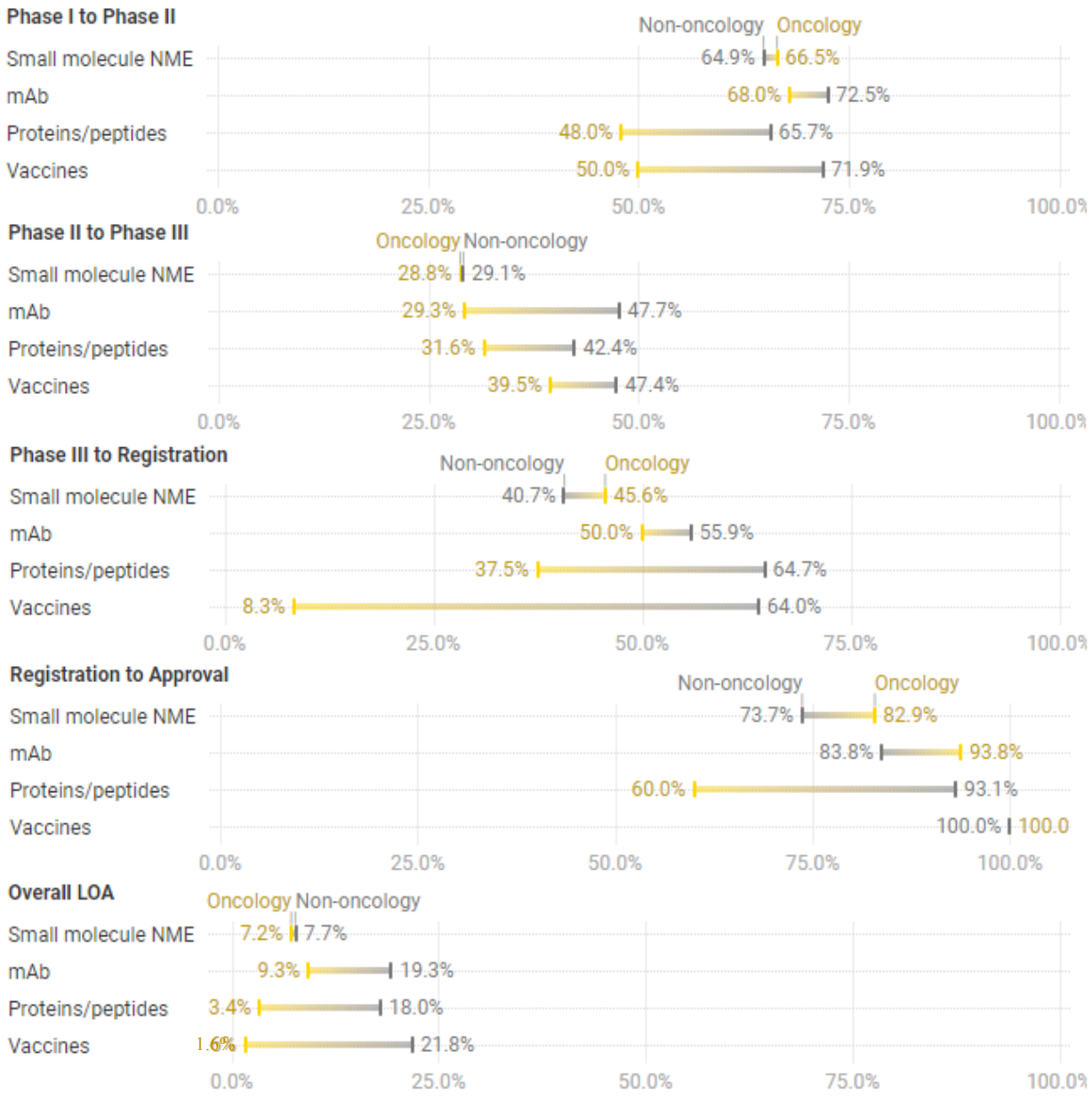


Figure 19. Comparison of Probability of Success for Oncology and Non-oncology Drugs by Drug Class
Data from Hay et al (2014) and compares oncological and non-oncological indications for the years 2003-2011. Yellow corresponds to oncology indications and gray corresponds to non-oncology indications. Both oncology and non-oncology vaccines had a Registration to Approval probability of success of 100%. LOA is an abbreviation of likelihood of approval.

As predicted, oncology vaccines had a far lower overall probability of success, especially in Phase III to Registration. Cancer vaccines are difficult to develop for a

multitude of reasons, including the presence of tumor-induced immunosuppressive mechanisms, difficulty in selecting appropriate patient populations and response criteria, and lack of specific identified and validated biomarkers[22]. While oncology and non-oncology small molecule NMEs had nearly the same overall LOA, the rest of the drug classes showed a decrease for oncology drugs relative to non-oncology products. This may be due to the increased understanding of the small molecule modality as well as the size of the molecule in targeting difficult tumors and therapeutic targets.

Autoimmune diseases can also be evaluated by their FDA drug class:

Figure 20 – Probability of Success for Autoimmune Diseases by FDA Drug Class

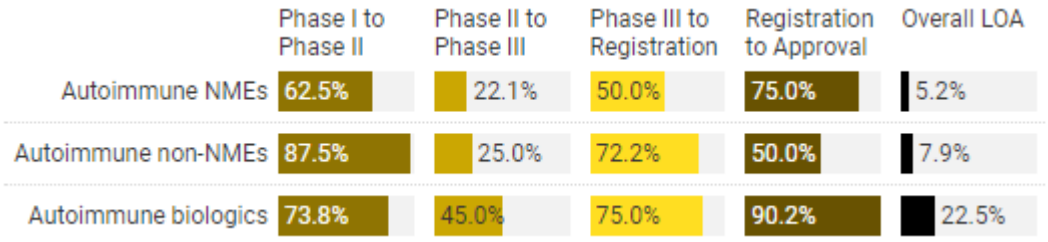


Figure 20. Comparison of Probability of Success for Autoimmune Diseases by FDA Drug Class
Data from Hay et al (2014) and presents the probability of success values for different autoimmune drug classes: NMEs, non-NMEs, and biologics. LOA is an abbreviation of likelihood of approval. The sample size in Registration to Approval is 8 in autoimmune disease NMEs and 12 in autoimmune disease non-NMEs. Autoimmune NMEs had the lowest probability of success across Phase I to Phase III, with as many as 22.9% between NMEs and biologics (as in Phase II). Autoimmune non-NMEs, however, had the lowest likelihood of approval at registration. These low probability of success values for autoimmune NMEs in Phase II are in part due to the low NME probability of success seen in rheumatoid arthritis and type II diabetes:

Autoimmune biologics had a considerably higher overall LOA than the other FDA drug classes and four times the overall LOA of autoimmune NMEs. It is possible that autoimmune biologics, as with all biologics, are more likely to be targeted therapies and experience greater preclinical scrutiny prior to advancing to clinical trials.

Success Rates by Origin

Finally, we can examine the drug origin—whether the compound was self-originated, licensed-in, or licensed-out—and its effects on the probability of success:

Figure 21 – Probability of Success by Drug Origin

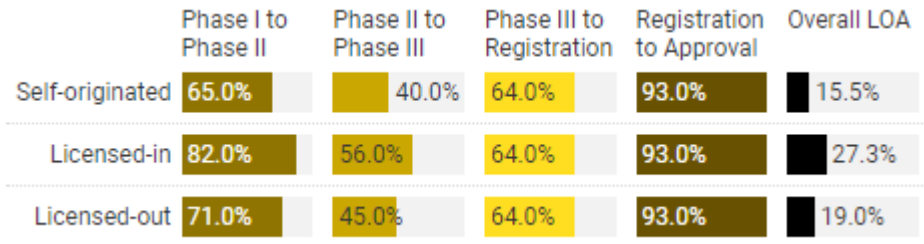


Figure 21. Comparison of Probability of Success by Drug Origin
Data from DiMasi et al (2010) and encompasses the self-originated, licensed-in, and licensed-out drugs from the years from 1993 to 2004. For both DiMasi et al (2010) and Smietana et al (2016), self-originated includes those products belonging to an acquired company. Of the three drug origin possibilities, self-originated compounds had the lowest likelihood of approval (15.5%), owing to their lower Phase I and Phase II

probability of success. Compounds that were licensed-in had the highest Overall LOA (27.3%) due to their higher Phase I and Phase II probability of success.

DiMasi et al (2010) defined licensed-in as those compounds licensed from companies outside the top 50 pharmaceutical firms. Licensed-out is defined as compounds licensed from a top 50 firm to a company outside that ranking.

The higher likelihood of approval for licensed-in compounds, particularly early in the clinical development process, likely is due to the rigorous screening performed by companies of external preclinical and early stage clinical assets. For example, if a drug showed promise in preclinical or Phase I, it is a more likely target for a licensing deal and therefore more likely to proceed to and potentially succeed in Phase II.

An evaluation of self-originated and licensed-in products emphasizes the higher probability of success of licensed-in products:

Figure 22 – Difference Between Self-Originated and Licensed-In

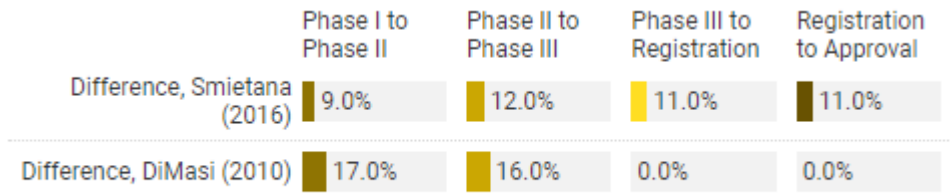


Figure 22. Comparison of Probability of Success for Self-Originated and Licensed-In Drugs
Data from Smietana et al (2016) and DiMasi et al (2010) and compares the self-originated and licensed-in drug probability of success values for the years from 1993 to 2004 (DiMasi) to the years from 2009 to 2014 (Smietana).

The increase in difference in the later stages of development and decrease in earlier stages of clinical development between DiMasi et al (2010) and Smietana et al (2016) may indicate a trend that more compounds are licensed-in following completion of Phase I or Phase II studies, therefore subjecting them to intense screening by licensing partners later in the clinical development process.

Effects of Probability of Success on Valuation Models

With these insights, let us see what the effect is of different probability of success values on a valuation model. In these, we will hold all other phase probability of success values to be equal and present only the example values used for the phase in question and their effects on the valuation. The values used for each phase are based on probability of success values mentioned in this report for different indications, orphan designations, biomarker usage, and partnering relationships.

As described early in the report, the benchmarks for overall average probability of success, as based on eight reviewed publications is:

Table 5 – Probability of Success Benchmarks

Table 5 – Probability of Success Benchmarks

Phase of Clinical Development	Probability of Success
Phase I to Phase II	61%
Phase II to Phase III	38%
Phase III to Pre-registration	63%
Registration to Approval	89%

In each example for each phase, when the phase probability of success value in the table equals the benchmark value, the row will be in gray.

To reach the example values, the following costs and timing for the various phases were used:

Table 6 – Costs and Timing for Pharmaceutical Development

Table 6 - Costs and Timing for Pharmaceutical Development			
Phase	Number of Patients	Costs ($k)	Timing (years)
I	35	$2,400	1.5
II	100	$20,000	2
III	800	$64,000	4
Regulatory cost	--	$10,000	1
Commercial manufacturing cost	--	$14.3/patient	--
Manufacturing investment	--	$10,000	--

Other parameters that were included in the valuation are listed below:

Table 7 – Parameters for Valuation Examples

Table 7 – Parameters for Valuation Examples	
Parameters	Value

Discount rate	12%
Tax rate	20%
Peak penetration	22%

Example 1 – Changes in Phase I Probability of Success

The range of Phase I probability of success values comes from the Phase I probability of success of oncology with no biomarkers (**Figure 13**) and an orphan vaccine indication (**Figure 11**):

Table 8 – Effects of Changes in Phase I Probability of Success on Total Risk Adjusted Valuation (rNPV)

Table 8 – Changes in Phase I Probability of Success					
Phase I (%)	**Corresponding Indication**	**Phase I Difference (%)**	**Valuation ($m)**	**Overall Difference ($m)**	**Overall Difference (%)**
89.5%	Orphan vaccines	N/A	$193	N/A	N/A
88%	Ophthalmology lead	1.5%	$190	$3	1.6%
82%	Licensed-in	6.0%	$177	$16	8.3%
76.3%	Orphan autoimmune/inflammation	5.7%	$164	$29	15.0%
66.7%	Non-NME, Hay (2014)	9.6%	$144	$49	25.4%
61%	Benchmark	5.7%	$131	$62	32.1%
54.8%	CNS, with biomarkers for patient selection	6.2%	$118	$75	38.9%
43.5%	Oncology, with biomarkers for patient selection	11.3%	$94	$99	51.3%

33.5%	Oncology, all biomarker usage	10.0%	$72	$121	62.7%
28%	Oncology, no biomarkers for patient selection	5.5%	$60	$133	68.9%

For Phase I, a decrease of 10% for Phase I probability of success results in a 2.2% decrease in overall likelihood of approval and a $22m decrease in valuation, amounting to an 11.5% decrease from the maximum valuation of $193m. Minute changes in the probability of success values can have consequences for the accuracy of the valuation, as a decrease of 1.5% for Phase I probability of success resulted in a $3m or 1.6% decrease in valuation.

Example 2 – Changes in Phase II Probability of Success

As Phase II is typically the phase where efficacy is first tested and has the lowest probability of success benchmark, we hypothesize that a change in its probability of success (with the other benchmark values staying constant) would have a greater effect on the valuation than a change in Phase I.

Therefore, a higher Phase II probability of success should result in a higher valuation than a higher Phase I value, all benchmarks being equal. The range of Phase II probability of success values comes from the Phase II probability of success of oncological indications with no biomarkers (**Figure 13**) to non-oncology orphan indications (**Figure 11**):

Table 9 – Effects of Changes in Phase II Probability of Success

Table 9 – Changes in Phase II Probability of Success					
Phase II (%)	**Corresponding Indication**	**Phase II Difference (%)**	**Valuation ($m)**	**Overall Difference ($m)**	**Overall Difference (%)**
81.2%	Orphan non-oncology, Hay (2014)	N/A	$294	N/A	N/A
70%	All orphan indications	11.2%	$252	$42	14.3%
66.7%	Orphan metabolic/endocrine	13.3%	$240	$54	18.4%

56.3%	Orphan CNS	10.4%	$200	$94	32.0%
46.2%	Orphan genitourinary	10.1%	$162	$132	44.9%
38%	Benchmark	8%	$131	$163	55.4%
30.2%	CNS, with no biomarkers	7.8%	$102	$192	65.3%
24.9%	Autoimmune/inflammation, no biomarkers	5.3%	$82	$212	72.1%
20.9%	Prostate cancer	4.0%	$67	$227	77.2%
16.2%	Oncology, no biomarkers	4.7%	$49	$245	83.3%

With the maximum Phase II and benchmark probability of success values, the valuation amount increases to $294m over the $163m reported for Phase I, due to their respective benchmark probability of success values (38% for Phase II in comparison to 61% for Phase I). As expected, the equivalent 10% decrease in Phase II probability of success results in a 3% change in overall likelihood of approval and a $38m decrease in valuation, amounting to a 13% decrease from the maximum valuation of $294m. As with Phase I, a small difference (3%) in Phase II success rate can result in a measurable decrease in valuation ($12m).

Example 3 – Changes in Phase III Probability of Success

As Phase III is the final stage prior to approval and evaluates a compound's therapeutic effect, a change in the probability of success in this phase would likely have the greatest effect on the valuation. The range of Phase III probability of success values comes from the Phase III probability of success of myelodysplastic syndrome (**Figure 8**) to musculoskeletal indications (**Figure 4**):

Table 10 – Effects of Changes to Phase III Probability of Success

Table 10 – Changes in Phase III Probability of Success					
Phase III (%)	**Corresponding Indication**	**Phase III Difference (%)**	**Valuation ($m)**	**Overall Difference ($m)**	**Overall Difference (%)**
80%	Musculoskeletal	N/A	$173	N/A	N/A

75.0%	Hematology	5.0%	$160	$13	7.5%
72.2%	Infectious disease	2.8%	$154	$19	11.0%
69%	Non-mAb proteins	3.2%	$146	$27	15.6%
63%	Benchmark	6.0%	$131	$42	24.3%
60.1%	Hay (2014)	2.9%	$124	$49	28.3%
50%	Vaccine drug class, Hay (2014)	10.1%	$100	$73	42.2%
38.5%	Colorectal cancer	11.5%	$72	$101	58.4%
26.1%	Non-small cell lung cancer	12.4%	$42	$131	75.7%
20%	Pancreatic cancer	6.1%	$27	$146	84.4%

The 10% decrease in Phase III probability of success did result in a greater decrease in valuation (13.9%) than in Phase I or Phase II, as expected. However, due to the higher benchmark value in Phase III, the maximum valuation when only changing Phase III results in a lower value ($173m) than for Phase II ($294m), the phase with the lowest benchmark value.

Example 4 – Changes in Registration to Approval Probability of Success

The range of Registration to Approval probability of success values comes from pancreatic cancer and renal cell carcinoma (**Figure 8**):

Table 11 – Effects of Changes to Registration to Approval Probability of Success

Table 11 – Changes in Registration to Approval Probability of Success					
Registration to Approval (%)	**Corresponding Indication**	**Registration Difference (%)**	**Valuation ($m)**	**Overall Difference ($m)**	**Overall Difference (%)**
100%	Renal cell carcinoma	N/A	$151	N/A	N/A
96%	Biologics, DiMasi (2010)	4.0%	$144	$7	4.6%

93%	DiMasi (2010)	3.0%	$139	$12	7.9%
90.2%	Lead endocrine	2.8%	$134	$17	11.3%
89%	Benchmark	1.2%	$131	$20	13.2%
85.1%	Non-oncology orphan, Hay (2014)	3.9%	$124	$27	17.9%
76.1%	Small molecule NME	9.0%	$108	$43	28.5%
70%	Breast cancer	6.1%	$97	$54	35.8%
66.7%	Head and neck cancer	3.3%	$91	$60	39.7%
50%	Pancreatic cancer	16.7%	$61	$90	59.6%

Compared to Phase I to Phase III, the effect of an increase in the Registration to Approval probability of success on the valuation is minimal due to the smaller spread between the maximum and minimum probability of success values (50%) and the even smaller difference between the benchmark and the maximum probability of success (11%). As such, the maximum valuation ($151m) is the lowest of the four phases, only $20m greater than the benchmark valuation of $131m.

Changes to the probability of success at any phase can result in small to substantial changes in the probabilities of success. While the difference is small (13.9% to 11.2% for registration), changes to the Phase III probability of success resulted in the largest changes in dollars and as well as percentage of the maximum valuation. The maximum valuation was seen with Phase II, as its benchmark probability of success was lowest (38%) while the maximum probability of success for the phase was 89.5% for all non-oncology indications.

Discussion

As expected, in the literature, oncology has one of the lowest Phase III and overall probabilities of success among the various therapeutic areas, an effect that is largely consistent across orphan disease status, biomarker usage, and modality. Contributing to this low probability of success is that Phase III clinical trials for oncology drugs require overall survival as a primary endpoint and many diseases lack well validated surrogate endpoints and biomarkers that will enable faster determination of efficacy and potentially faster approval. Additional contributing factors include lack of proper patient stratification and minimal understanding of many of the underlying pathways and mechanisms of disease, though these reasons may also be consistent for other

therapeutic areas as well. With the accelerating development and focus in oncology as well as the identification of new pathways of disease and advent of new modalities (such as cancer vaccines and cell and gene therapies), continued examination of oncology clinical trial success will be highly important in the years to come.

Another interesting observation was while it was expected that lead indications would have higher probabilities of success than nonlead indications, the result was not consistent across the various therapeutic areas. Lead indications are expected to have higher success rates due to the indication having the strongest commercial and scientific rationale for proceeding to clinical trials. These lead indications would be expected, as Hay et al (2014) note, to involve more homogenous patient populations and a better understood mechanism of action and regulatory path than other indications for which a molecule is tested. However, it is also possible that subsequent clinical trials for other indications resulted in a higher overall probability of success following an improved understanding of the molecule or efficacy or safety failures for the lead indications. As drug makers continue to seek approval for a single molecule in multiple indications, it grows increasingly important to select indications for which there is the greatest scientific and commercial rationale.

The results from 1993 to 2015 revealed many important details not only about the therapeutic areas, lead indication status, oncology indication, orphan disease status, drug classes, or drug origin as reviewed in this paper, but also about the way clinical probability of success has changed over the past 22 years and the effect of sample resources, methodologies, and sizes on the results. In some instances throughout this paper, it is clear that indication-specific or biomarker usage breakdowns resulted in very limited sample sizes, making it difficult to draw conclusions. DiMasi et al (2010) differed from the other publications by covering a significantly earlier time frame and focusing on only the top 50 companies, which likely contributed to differences for oncological tumor categories and the comparison between small molecules and biologics relative to the more recent publications. Methodology differences, explained in more detail in **Appendix: Source Methodology**, resulted in discrepancies between Wong et al (2018) and the other publications in areas like biomarker usage for patient selection and oncology orphan indications, even if the same time frame was covered.

The increasing identification, evaluation, and usage of biomarkers for patient selection and their role in improving diagnosis and treatment of orphan diseases should ideally result in an improvement overall probability of success for the major therapeutic areas. Continued assessment of probability of success values will be crucial to determine how advances in science and changes in the regulatory landscape will affect the likelihood that a company's investment in a drug will result in an approval.

Conclusions

Probability of success is an important input in a valuation model. The benchmark values of 61%, 38%, 63%, and 89%—for Phases I, II, III, and registration, respectively—have largely stayed consistent since the start of the 21st century. The choice between a benchmark value and an ideal molecule—such as an orphan cardiovascular indication—could result in a difference of $348m in valuation. To reach as accurate as possible valuation for a company, portfolio, or compound, the right set of probability of success values should be used for that therapeutic area, oncological indication, orphan designation, biomarker usage type, and drug class. As interest grows in new moieties, biomarker use, and digital health aids, the probability of success values will continue to change and inform strategic business decisions.

Appendix: Source Methodology

The papers used differed in their sample size, years evaluated, and methodology.

The predominant methodology, described by Wong et al (2018) as "phase-by-phase", evaluates whether a phase transition occurs. The "phase-by-phase" methodology computes the ratio of observed phase transitions (i.e. Phase I to Phase II) to the total number of observed drug development programs. This methodology, as described, has the tendency to remove—or count as terminated—those trials that progressed directly from Phase I to Phase III (often due to adaptive trials or breakthrough methodology), which could therefore underestimate the probability of success. For simplicity, we consider those publications that explicitly mention performing a phase transition-focused calculation (such as following Phase x to Phase x + 1) as "phase-by-phase".

In comparison, the "path-by-path" approach, as described by Wong et al (2018), evaluates whether a drug development project progresses, regardless of indication, and therefore counts those compounds that progress directly from Phase I to Phase III as a success. This methodology therefore tends to inflate the probabilities of success in Phase I and Phase II (as seen for Phase II in **Error! Reference source not found.**). The tendency is seen particularly when a rolling-window computation is used, as the model tends to continue to input an already completed and counted phase completion continually over the subsequent smaller windows of time. For simplicity, we consider those publications that explicitly mention including missing Phase II trials (as in Wong et al, 2018 and Smietana et al, 2016) as "path-by-path".

For both methodologies, the overall probability of success is calculated by multiplying the individual phase probabilities. We present a summary of each paper's data source, compounds analyzed, years evaluated, and methodology (summarized as "phase-by-phase" or "path-by-path"):

Table 12 – Source Summary and Methodology

Table 12 – Comparison between Sources					
Publication	**Years**	**Compounds**	**Data Source**	**Companies**	**Methodology**
DiMasi et al, 2010	1993-2004	1,738	IMS R&D database	Top 50 pharmaceutical companies (by sales)	Phase-by-Phase
Paul et al, 2010	Through 2007	Unknown	KMR Group, Eli Lilly R&D pipeline data	13 large pharmaceutical companies	Unknown
Hay et al, 2014	2003-2011	4,451	BioMedTracker	835 companies	Phase-by-Phase
Smietana et al, 2015	2007-2012	Unknown	Informa Pharmaprojects	All novel compounds	Unknown
DiMasi et al, 2016	1995-2007	1,442	IMS R&D Database	Top 50 pharmaceutical companies (by sales)	Unknown (calculates drugs approved or discontinued in each phase)
Smietana et al, 2016	1996-2014	9,200+	Informa Pharmaprojects	Unknown	Path-by-Path (counts Ph I to Ph III transitions as successes)
Thomas et al, 2016	2006-2015	7,455	BioMedTracker	1,103 companies	Phase-by-Phase
Wong et al, 2018	2000-2015	21,143	Informa Trialtrove and Pharmaprojects	185,994 trials from industry and non-industry	Path-by-Path

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