Probabilities of success (POS) play a key role in determining the distribution of resources by both investors and the pharmaceutical industry. Resources such as time, money and personnel are more likely to be directed toward programs in categories with acceptable rates of success. What is considered acceptable may, of course, vary between companies and other decision-makers. With the increased focus on development of antibody therapeutics, it is important for stakeholders to understand the utility, and limitations, of POS values such as cumulative approval success rates and clinical phase transition probabilities. A key point is that cumulative approval success rates are derived from data for only those candidates with known fates (either approved or terminated), but clinical phase transition probability calculations include data on the status of all candidates.

POS values for various cohorts of monoclonal antibody (mAb) therapeutics have been reported previously. For mAb POS, a key consideration is the source of the protein sequence. Data for humanized and human mAbs must be analyzed separately because, overall, these molecules display improved safety and efficacy profiles compared to murine and chimeric versions. Humanized mAbs comprise the ‘canonical’ cohort because a large number (>150) of these candidates have entered clinical study over the last two decades (1988–2008), and 12 have been approved (Table 1). However, ultimate fates (approval or termination) are known for only about half, and the cumulative approval success rate for the entire cohort of humanized mAbs will only be an estimate until the fates of all the molecules have been decided. The current cumulative approval success rate estimate for humanized mAbs is 17%.2

It is important to note that time plays an essential role in POS calculations. In general, clinical study and regulatory review periods for therapeutics are lengthy, and mAbs are not exceptional in this regard. The mean (median) for the combination of the clinical and US Food and Drug Administration (FDA) approval phases for 23 mAbs (Table 1) is currently 8 (7) years. This has important implications for POS calculations for mAb cohorts that include high percentages of candidates that have entered clinical study within the past seven or eight years. Candidates that have entered clinical study since 2001 have not had sufficient time, on average, for approval, but might have been terminated for a variety of reasons. This suggests that there is a downward bias in cumulative success rates for cohorts that include candidates that recently entered clinical study. Indeed, the cumulative success rate for humanized mAbs changes dramatically when the cohort is divided into two groups: candidates that entered clinical study during 1988–1996 (n = 30; eight approved) and 1997–2008 (n = 125; two approved). Ultimate fates are known for 87% of the older candidates, and the cumulative success rate for the cohort is 31%. However, ultimate fates are known for only 33% of the newer candidates, and because many have not been in clinical study long enough to accumulate the data needed for approval, the cumulative success rate is 5%. This value will rise to 9% if the two humanized mAbs in FDA review (Table 1) are approved.

Clinical phase transition probabilities are another important measure of the success of a cohort such as humanized mAbs. Whereas cumulative approval success rates include data only for candidates that are either approved or terminated, clinical phase transition probabilities take the status of all candidates into account. It is critical to understand the relationship between the two parameters in order to interpret POS values appropriately. The mathematical product of the phase transition probabilities will exactly equal the cumulative success rate only when the fates of all the candidates are known. In practice, the two values will converge as the percentage with known fates goes to 100%. When the fates of fewer than 50% are known, then the values can be quite different. One reason for this phenomenon is that candidates that will ultimately be discontinued remain, technically, at Phase 2 for long periods while the company decides whether to advance these perhaps marginal candidates into expensive Phase 3 studies, or attempts to partner or out-license the projects. In these cases, the candidates contribute in a positive way to the Phase 1 to Phase 2 transition probability, and inflate the mathematical product, but are not yet included in the cumulative success rate calculation because they have not been officially terminated.

A comparison of phase transition probabilities for humanized mAbs with the cumulative approval success rates provides a good example of the phenomenon. The values for candidates that entered clinical study during the three periods 1988–2008, 1988–1996 and 1997–2008 are quite similar: Phase 1 to 2 transition probabilities were 83, 90 and 80%, respectively; Phase 2 to 3 transition probabilities were 48, 50 and 46%, respectively; Phase 3 to FDA review transition probabilities were 75, 73
Probabilities of success for antibody therapeutics

The mathematical products of the phase transition probabilities for the three cohorts are similar: 30, 33 and 29%, respectively, despite the fact that the current cumulative approval success rates vary (17, 31 and 5%, respectively). This suggests that, so far, the newer candidates are proceeding through clinical studies at a pace that is similar to the older candidates. However, the cohort of candidates that entered clinical study recently (n = 125) is much larger compared to the cohort of candidates that entered clinical study during 1988–1996 (n = 30), and many are in early clinical studies. It remains to be seen whether a similar proportion of the newer candidates will ultimately be approved.

Additional complexity arises when POS values from various sources are compared. Such comparisons should be done cautiously because factors such as variations in methodology, time-frame, and cohort inclusion criteria can have dramatic effects on the calculated results. End users, including investors and strategic planners, should carefully consider whether a distinction between a cumulative approval success rate and the mathematical product of phase

| Table 1 | Therapeutic monoclonal antibodies in FDA review or approved |
|---------|-------------------------------------------------------------|
| Generic name | Trade name | Type | Indication under consideration or first approved | FDA approval year |
| Raxibacumab | Pending | Human IgG1 | Anthrax infection | Pending |
| Tocilizumab | Actemra* | Humanized IgG1 | Rheumatoid arthritis | Pending |
| Ustekinumab | Stelara* | Human IgG1 | Psoriasis | Pending |
| Motavizumab | Numax* | Humanized IgG1 | Prevention of respiratory syncytial virus infection | Pending |
| Canakinumab | Pending | Human IgG1 | Muckle-Wells syndrome | Pending |
| Denosumab | Pending | Human IgG2 | Bone loss | Pending |
| Ofatumumab | Arzerra* | Human IgG1 | Chronic lymphocytic leukemia | Pending |
| Golimumab | Simponi | Human IgG1 | Rheumatoid and psoriatic arthritis, ankylosing spondylitis | 2009 |
| Certolizumab pegol | Cimzia | Humanized Fab | Crohn disease | 2008 |
| Eculizumab | Soliris | Humanized IgG2/Fab | Paroxysmal nocturnal hemoglobinuria | 2007 |
| Panitumumab | Vectibix | Human IgG2 | Colorectal cancer | 2006 |
| Ranibizumab | Lucentis | Humanized IgG1 Fab | Macular degeneration | 2006 |
| Natalizumab | Tysabri | Humanized IgG4 | Multiple sclerosis | 2004 |
| Bevacizumab | Avastin | Humanized IgG1 | Colorectal cancer | 2004 |
| Cetuximab | Erbitux | Chimeric IgG1 | Colorectal cancer | 2004 |
| Efluzumab | Raptiva | Humanized IgG1 | Psoriasis | 2003# |
| Tositumomab-131 | Bexxar | Murine IgG2a | Non-Hodgkin lymphoma | 2003 |
| Omalizumab | Xolair | Humanized IgG1 | Asthma | 2003 |
| Adalimumab | Humira | Human IgG1 | Rheumatoid arthritis | 2002 |
| Ibritumomab tiuxetan | Zevalin | Murine IgG1 | Non-Hodgkin lymphoma | 2002 |
| Alemtuzumab | Campath-1H | Humanized IgG1 | Chronic myeloid leukemia | 2001 |
| Gemtuzumab ozogamicin | Mylotarg | Humanized IgG4 | Acute myeloid leukemia | 2000 |
| Trastuzumab | Herceptin | Humanized IgG1 | Breast cancer | 1998 |
| Infliximab | Remicade | Chimeric IgG1 | Crohn disease | 1998 |
| Palivizumab | Synagis | Humanized IgG1 | Prevention of respiratory syncytial virus infection | 1998 |
| Basiliximab | Simulect | Chimeric IgG1 | Prevention of kidney transplant rejection | 1998 |
| Daclizumab | Zenapax | Humanized IgG1 | Prevention of kidney transplant rejection | 1997 |
| Rituximab | Rituxan | Chimeric IgG1 | Non-Hodgkin’s lymphoma | 1997 |
| Abciximab | Reopro | Chimeric IgG1 Fab | Prevention of blood clots in angioplasty | 1994 |
| Muromonab-CD3 | Orthoclone | Murine IgG2a | Reversal of kidney | 1986 |

Note: Information current as of May 15, 2009. *Proposed trade name; #Voluntarily withdrawn from US market in April 2009. FDA, US Food and Drug Administration. Source: Tufts Center for the Study of Drug Development
transition probabilities has been made, and whether sufficient information about the cohort and methodology has been provided so that the POS values presented can be clearly understood.

References
1. Nelson AL, Reichert JM. Development trends for therapeutic antibody fragments. Nat Biotechnol 2009; 27:331-7.
2. Reichert JM. Monoclonal antibodies as innovative therapeutics. Curr Pharma Biotechnol 2008; 9:423-30.
3. Reichert JM, Rosenweig CJ, Faden I.B, Dewitz MC. Monoclonal antibody successes in the clinic. Nat Biotechnol 2005; 23:1073-8.
4. Reichert J, Pavlou A. Monoclonal antibodies market. Nat Rev Drug Disc 2004; 3:383-4.
5. Reichert JM. Therapeutic monoclonal antibodies: trends in development and approval in the US. Curr Opin Mole Ther 2002; 4:110-8.
6. Reichert JM. Monoclonal antibodies in the clinic. Nat Biotechnol 2001; 19:819-22.