With comprehensive information on endpoints, timelines, populations and safety results readily available as a benchmark, the FDA approval process can offer cancer pivotal trials real flexibility.

Approval Requirements

As a rule, the FDA recommends that applications include data from “at least two adequate and well-controlled clinical trials” as a condition of standard drug approval (3). In cancer, however, the high degree of unmet medical need and the urgency of offering new treatments for potentially fatal diseases mean that approvals are based on a wide range of clinical data packages.

Table 1: Cancer drug approvals by cancer type 2005-2011

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Cancer</th>
<th>Approved indications</th>
<th>Percentage of total</th>
<th>Orphan drug indications</th>
<th>Percentage of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematologic</td>
<td>Leukaemia</td>
<td>13</td>
<td>16</td>
<td>8</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Leukaemia and lymphoma</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Lymphoma, excluding NHL</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Myelodysplastic syndrome</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Non-Hodgkin lymphoma</td>
<td>8</td>
<td>10</td>
<td>1</td>
<td>3</td>
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<td></td>
<td>Haematologic total</td>
<td>33</td>
<td>40</td>
<td>19</td>
<td>56</td>
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<tr>
<td>Solid tumour</td>
<td>Brain cancer</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Breast cancer</td>
<td>9</td>
<td>11</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Cervical cancer</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Colorectal cancer</td>
<td>3</td>
<td>4</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal cancer</td>
<td>4</td>
<td>5</td>
<td>2</td>
<td>6</td>
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<tr>
<td></td>
<td>Head and neck cancer</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>6</td>
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<tr>
<td></td>
<td>Kidney cancer</td>
<td>7</td>
<td>8</td>
<td>3</td>
<td>9</td>
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<tr>
<td></td>
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<td>1</td>
<td>1</td>
<td>3</td>
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<tr>
<td></td>
<td>Lung cancer</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td>3</td>
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<td>Ovarian cancer</td>
<td>1</td>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pancreatic cancer</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>0</td>
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<td></td>
<td>Prostate cancer</td>
<td>4</td>
<td>5</td>
<td>-</td>
<td>0</td>
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<tr>
<td></td>
<td>Skin cancer</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Thyroid cancer</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
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<tr>
<td></td>
<td>Solid tumour total</td>
<td>50</td>
<td>60</td>
<td>15</td>
<td>44</td>
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<td>Total</td>
<td></td>
<td>83</td>
<td>100</td>
<td>34</td>
<td>100</td>
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</table>
This is demonstrated in Table 2, which shows that the “two adequate and well-controlled trials” standard is actually an unusual occurrence in cancer, as only two per cent of all indications received approval using this approach. Indeed, approved applications have been based on pivotal trials ranging from as little as a single Phase 1 pharmacokinetic study (asparaginase *Erwinia chrysanthemi*, approved in 2011 as part of a combination regimen for acute lymphoblastic leukaemia) to as much as three separate Phase 3 trials (rituximab’s 2006 approval for use with CHOP chemotherapy in newly diagnosed non-Hodgkin lymphoma patients).

Despite the variance, certain thresholds are evident. For example, 75 per cent of all applications and 56 per cent of orphan indications were directly supported with at least one Phase 3 trial. Standards are predictably higher for non-orphan indications, where 88 per cent of applications included a Phase 3 trial. Of indications approved without Phase 3 support, most were for patients who had failed or who demonstrated intolerance to earlier lines of therapy, which is understandable given the limited treatment options available to these groups.

In addition to demonstrating the range of required data, Table 2 also reveals that 59 per cent of all indications were approved with a single Phase 3 trial. Nearly three-quarters of all non-orphan drugs fall in this category, and it is the most common scenario for orphan drugs as well. In the absence of specific guidance from regulatory agencies, this category may serve as the best available proxy for establishing the scope of a clinical trial programme necessary to gain approval.

### Pivotal Trial Design

The database also captures elements of pivotal trial design. Using comparisons between solid tumours and haematological malignancies, the following explore several of the more important design features: primary endpoints, number of arms and control types.

#### Primary Endpoints

Overall survival, defined as the time from randomisation until death from any cause, is the FDA’s gold standard for drug approval in the cancer field. From a development standpoint, however, it is the most difficult and costly endpoint to demonstrate as it requires higher patient populations and longer follow-up periods. As we have seen in the preceding section, the FDA is often willing...
to accept less than gold standard evidence when
doing so will make new therapies available if the data is
sufficient to show that these new therapies are both safe
and effective.

Indeed, as shown in Table 3, overall survival served as the
primary endpoint in only 18 per cent of all pivotal trials during
our time period. Although it was the most common primary
endpoint in solid tumours, it still represented just one third of
such trials, barely edging out progression-free survival, which
was the primary endpoint in 29 per cent of solid tumour pivotal
trials. More striking is its near-total absence in haematologic
malignancies, where only four per cent of pivotal trials featured
overall survival as a primary endpoint. In these cancers, response
rate and the closely related duration of response/clinical benefit
are the predominant primary endpoints, having been used to
support 59 per cent of all approvals.

Number of Arms
Figure 2 shows the frequency of multiple and single arm
trials in cancer pivotal trials. Two-arm trials dominate the solid
tumour category, with 84 per cent of all studies falling into
this category and the remainder being split equally between
two and three-arm trials. The picture is quite different
in haematologic malignancies, however, where single arm trials
account for 49 per cent of all haematologic pivotal studies and
are as common in these cancers as two arm trials. It is important
to note that the data in Figure 2 is based on individual pivotal trials
and, as we have seen, indications are often approved on the basis
of more than one trial. However, there were eight approvals in
our time period that were made on the basis of a sole, single arm
trial. Most were for haematologic cancers, and these applications
tended to be for conditions with small populations or for use
in second line or later patients.

Also of interest is the five per cent of trials in the dataset that
featured three arms, all but one of which were in the solid
tumour category. Three arms were used to test different doses
of the investigational drug or in cases where the agent was
included in both monotherapy and combination regimens. In
each of these instances, a single arm received approval – a fact
that suggests more extensive testing at an earlier phase might
have allowed for cost savings through the elimination of the
third arm. This must be weighed against the additional time
required to conduct further research before moving into the
pivotal study. However, three-arm trials also slow the process
by diverting scarce patients into an arm that will ultimately
be discarded. Data on recruitment times and accrual rates,
discussed later in this article, may assist planners in evaluating
the time trade-off between conducting additional small studies
or moving directly into the pivotal trial with a three arm study.

Control Types
Selecting a comparison arm for cancer trials is generally more
challenging than in other types of drug development. On the
one hand, there is a desire to demonstrate the treatment’s
effect as clearly as possible, something that is best done
with a placebo control. On the other hand, review boards are
often reluctant to approve these types of trials, as there are serious
ethical issues involved in featuring a placebo arm with patients
suffering from a potentially fatal disease. Instead, common practice
calls for using an active control (usually the existing standard-of-
care regimen) in the control arm with the investigational agent
used either in combination with the standard-of-care or, in cases
where more data is available, as monotherapy.
In Figure 3 we see how these general rules are applied in practice. If we ignore single arm trials in haematologic malignancies for the moment, active controls do in fact serve as the most common type of comparison arm for both cancer types. There are also, however, a fair number of placebo-controlled pivotal trials, particularly in the solid tumour area. Usually, these were for patients who had failed earlier lines of therapy, but this was not always the case as two trials (both in renal cell carcinoma) achieved first-line indications via placebo-controlled trials. Placebo-controlled trials were substantially more likely to be used in monotherapy (82 per cent) than in combination therapy trials (18 per cent). This is somewhat surprising given the aversion to giving cancer patients placebo-only treatment, but may, at least in part, be reflective of the fact that there are no existing standards-of-care for certain advanced cancers.

**Trial Performance Metrics**

In addition to understanding key design characteristics, planners also need to know how their trials are likely to perform in the implementation stage. Several key findings can be drawn from the database regarding time from pivotal trial initiation to approval, accrual rates and trial placement patterns.

**Development Time**

Figure 4 shows the median time required from pivotal trial initiation (defined here as the date of first patient enrolment) to FDA approval by cancer type (several cancers are excluded because of limited data). For the cancers shown, the overall median time is approximately 63 months or a little over five years. However, this ranges considerably from a low of 36 months for kidney cancer to a high of more than 100 months in skin cancer trials. The analysis suggests that these variations are driven by a combination of several factors including the size of the available population, the number of competitive trials taking place at the same time, and how the existing standard-of-care is viewed.

**Accrual Rates**

Several of the factors that slow development times are beyond the planner’s control. Subject to constraints on the budget and site availability, however, it is generally possible to speed the process by increasing the number of locations hosting the trial. The information in Figure 5 (see page 34) is of interest for this reason as it shows the median accrual rate for various types of cancer. (As with the time to approval data, some cancer types are not shown.) Note that accrual rate is defined as the number of patients recruited per site per month and the number of total months is based on the period from first patient enrolled to last patient enrolled.

The median accrual rate for the included conditions is 0.23 patients per site per month. Using this information, a hypothetical trial with a recruitment goal of 1,000 patients could expect to achieve full enrolment in 43.5 months with 100 sites and 34.8 months with 125 sites. Of course, there is no such thing as a ‘median cancer’ and, as we have seen with the time to approval data, recruitment rates vary considerably between conditions. Unsurprisingly, those with the fastest
times to approval also tend to have the highest accrual rates.

Pivotal Trial Location
A great deal of attention has been devoted to the globalisation of clinical trials in recent years, particularly as this relates to placement in developing countries. In that context, the information in Figure 6 is interesting as it shows that, at least among the pivotal trials supporting cancer drug approval in our time period, three quarters of all sites were in North America or western Europe while China and India – locations that are at the heart of the debate over globalisation – had only two per cent of all sites combined. Considering that trials in emerging countries are generally able to recruit patients more rapidly than is the case in more traditional locations, an argument can be made that there is too little rather than too much clinical research taking place in emerging countries. This is especially relevant given what we have seen about accrual rates.

Conclusion
Analysis of the database reveals a number of valuable facts about cancer pivotal trials. Most notably, we have seen that these studies are more varied and the FDA approval process is more flexible than may be commonly understood. For example, in comparison to other drug types, it is relatively rare for an oncology agent to be approved based on two or more Phase 3 trials and overall survival, the preferred primary endpoint, is used in only a minority of all cases, and almost never in haematologic malignancies.

Further, while it is known that these trials take a considerable amount of time, we now have specific measurements to assist in the forecasting process and can see how changing the number of sites is likely to affect the accrual period. Finally, the very limited level of trial placement in emerging locations suggests that there is an opportunity to speed the development cycle while still restricting participation to the highest quality institutions in these countries.

References
3. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, Food and Drug Administration, May 2007

About the author
Todd Clark is the President of Value of Insight Consulting. Over the past 20 years he has worked with leading drug and biotech companies, advising them on global issues regarding clinical trial design, life cycle management, regulatory compliance, marketing strategy and more.

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