Decision-making associated with drug candidates in the biotechnology research and development (R&D) pipeline

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Abstract

This research investigated the issues and methods of analysis considered by executives when managing biotechnology drug candidates within the research and development (R&D) pipeline. A mail survey was developed to assess: (1) factors considered during clinical trials; (2) sources of funding for R&D; (3) analytic tools used in decision-making; and (4) the use and application of pharmacoeconomics, and targeted primarily Chief Financial Officers (CFO) within 396 biotechnology firms in the United States (US). Consistent with prior research on CFOs, a response rate of 7.5 per cent was achieved and respondents generally represented smaller biotechnology companies valued below US$100m. Findings indicated that regulatory and capital requirements as well as investor expectations were important factors throughout clinical phase trials. Venture capital and capital/securities markets were the most commonly used sources of R&D capital. The most frequently cited decision-making techniques used included prior experience/intuition/human judgment, net present value (NPV), and internal rate of return (IRR). Pharmacoeconomic methods were utilised at every stage of R&D and applied to the management of R&D pipelines in addition to aspects of product pricing and reimbursement. Overall, these results reflect the nature of risk and uncertainty associated with pharmaceutical and biotechnology R&D. Although the use of past experience/intuition/human judgment was most common for decision-making, methods based upon discounted cash flow (DCF) approaches were also employed frequently, as was the use of pharmacoeconomics. The implications of this work should seek to catalyse the development and utilisation of robust methods to manage drug pipelines such that senior executives are afforded optimal recommendations when attempting to hedge risk and maximise return.

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INTRODUCTION

In their discussion of executive leadership, Garvin and Roberto[1] commented that 'decision-making is arguably the most important job of the senior executive and one of the easiest to get wrong'. Within the biotechnology and pharmaceutical sectors,

decision-making surrounding research and development (R&D) is particularly important given the high risk and uncertainty associated with bringing a new drug to market.[2,3] Addressing recent trends in drug development, the October 2006 United States (US) Congressional Budget Office report on pharmaceutical R&D indicated increasing R&D expenditures, decreasing US Food and Drug Administration (FDA) approvals, and lengthier clinical trials.[3] Although a requisite to have a marketed drug, R&D efforts do not provide any guarantee that a product may achieve FDA approval, or even be adopted by and paid for by consumers. In itself, maintaining a continuous product pipeline has been suggested as a key contributor of sustainable growth within the biotechnology and pharmaceutical industries.[4] As such, the decision-making processes required during R&D are critical to firm performance.[2] Valentine[5] stated, quite succinctly, that the management of R&D portfolios ultimately determines whether a drug company succeeds or fails.

The consequences of decisions concerning R&D often have long-term ramifications, particularly when considering the time and capital required for a product to reach FDA approval.[6] Concerning capital, Fildes[7] noted that a primary objective for small biotechnology firms was to raise funds required for pipeline R&D. Although these monies may be leveraged from numerous sources, venture capital funding or the formation of a strategic alliance with a larger pharmaceutical company has been identified to be of key importance to smaller biotechnology companies.[4,8,9,10]

The ability to strategically manage investment opportunities constitutes a vital function of senior executives. In this context, Lam[11] stressed the importance of high-level management to make 'go/no-go decisions' (ie key strategic inflection points wherein a decision is made to either continue a project or to immediately terminate it). In biotechnology or pharmaceutical R&D, go/no-go decisions often require consideration of broad economic and financial efficiencies (eg tradeoffs regarding maximising return on investment versus hedging risk).[2] Concerning overall decision-making, Bonabeau[12] emphasised that higher levels of reasoning and analysis are necessary when the complexity and the number of options embodied within decision-making increases. Furthermore, Garvin and Roberto[1] commented that decision-making should be viewed as a dynamic process that changes over time, rather than as a single static event. Despite the importance of making optimal decisions while managing drug pipelines, a 1997 marketing report conducted by CMR International of 28 pharmaceutical companies indicated that the most common method reported to begin either preclinical research or full-scale development was that of human judgment rather than any formal analytic method.[13]

Focusing more specifically on the formal analysis of capital budgeting decisions, Loch and Bode-Greuel[14] discussed the difficulty of determining financial values of R&D project platforms due to their high levels of risk and uncertainty. Overall, the most theoretically sound capital budgeting tools utilise discounted cash flow (DCF) techniques, which involve assessments of future cash streams given assessments of the opportunity cost of capital.[9,15] Although DCF techniques are robust across a number of conditions and are generally recommended by academics, it has also been noted that these techniques may not necessarily incorporate the flexibility required to evaluate projects of extremely high risk or growth potential.[14,15] In these latter instances, extensions of Black–Scholes option models (ie real options) may be considered to assess project failure or growth potential.[14,15,16,17,18] Additional methods such as decision analyses, simulations, or genetic algorithms may also be considered to assess risk and returns relating to R&D portfolios to aid in high-level executive decision making.[2]

An emerging methodology to augment capital budget decision making in biotechnology and pharmaceutical R&D is pharmacoeconomics, broadly defined as 'the description and analysis of the costs of drug therapy to health care systems and society' and often exemplified as comparative cost-effectiveness or cost–benefit analyses.[19,20,21] DiMasi *et al.*[19] reported that over half of large

pharmaceutical companies occasionally utilised pharmacoeconomics for R&D decision making (eg licensing, pipeline, go/no-go decisions), while approximately half of small firms never used the methodology.

Given the aforementioned importance associated with R&D and senior executive decision making, the purpose of the current research endeavour was to investigate issues and methods of analysis considered when managing biotechnology drug candidates within the R&D pipeline. More specifically, the objectives were to examine factors of importance during clinical phase trials, the sources of capital funding sources used to leverage R&D, and the use and application of decision-making tools and pharmacoeconomics among biotechnology companies in the US.

METHODS

Sample, survey instrument, and mailing procedure

A cross-sectional design was used for data collection in this anonymous survey investigation, wherein a study-specific questionnaire was developed to target chief financial officers (CFOs) within the biotechnology sector or, in instances wherein no formal CFO was identifiable, the chief executive officer or business and development officer. The pool from which potential respondents were drawn comprised of members of the Biotechnology Industry Organisation. All members that were either public or private firms that produced a pharmaceutical or biotechnology product were included in the investigation's sample.

The study-specific survey instrument was developed for this investigation to assess numerous aspects of biotechnology R&D. A mixture of response sets, including five-point Likert scales (ie bounded by: Very Unimportant = 1 to Very Important = 5, Strongly Disagree = 1 to Strongly Agree = 5, and Never = 0 per cent to Always = 100 per cent) were employed to measure:

- firm demographics (ie year-end capitalised financial value of the firm, total R&D expenditures for the prior fiscal year, and number of research scientists actively engaged in R&D);
- general statements concerning R&D (ie perceived understanding of the risk and uncertainty of R&D by governmental policymakers, perceived understanding of the value of biotechnology agents by healthcare organisations, the importance of intellectual property, and achieving the cost of capital as representing a core aspect of firm operations);
- factors considered during early- versus late-clinical phase trials (ie capital requirements, formulary adoption, competitor activity, projected peak sales, regulatory requirements, and investor expectations);
- funding sources used to leverage capital for drug R&D (ie company sales revenue, strategic alliances, federal government, capital/securities markets, and venture capital);
- formal and informal analytic tools used to assist drug pipeline decision making prior to FDA approval (ie past experience/ intuition/human judgment, net present value (NPV), internal rate of return (IRR), real options, payback period/ discounted payback period, decision analysis/decision trees, sensitivity analysis, economic value-added (EVA®) analysis, and accounting rate of return); and
- use and application of pharmacoeconomics (ie single most common source of pharmacoeconomics expertise utilised, percentage of drugs candidates undergoing formal pharmacoeconomic evaluation, stage of R&D that pharmacoeconomics is first considered, and R&D or marketing component wherein pharmacoeconomics is applied (licensing, initial pipeline decisions, go/no-go decisions during clinical trials, pre-approval pricing and reimbursement, and post-approval pricing and reimbursement)).

In addition to these aforementioned domains, the following were included for privately

held firms addressing the following aspects of venture capital:

- general statements concerning venture capital companies (ie involvement in direct management of the firm, contacts stemming from venture capital company's to fund R&D, and the role of performance benchmarks (eg targets, deadlines) within contracts);
- number of venture capital companies used in the firm's initial funding; and
- stage of R&D that venture capital is considered most important.

Upon completion of the draft questionnaire by the investigators, face and content validity was addressed through consultation of both university faculty and corporate executives. The final survey instrument was a 16-page booklet consisting of either: (1) 12 questions with 41 items for public firms listed on a major stock market exchange; or (2) 15 questions with 46 items for privately held companies. Institutional Review Board (IRB) for the study was obtained through the University of Arizona Human Subjects Protection Program.

The mailing procedure employed in the study followed a modified form of the *Total Design Method* that included two mailings of a survey packet (consisting of a cover letter, and business-reply, postage paid survey instrument) and two reminder postcards.[22] All mailings were addressed directly, by name, to potential respondents. Mailings occurred with two-week intervals and consisted of an initial survey packet (24th February, 2006), an initial reminder postcard (3th March, 2006), a second survey packet (24th March, 2006), and a final reminder postcard (7th April, 2006). Only those surveys that were returned by 26th May, 2006 were included in the final analyses.

Data analysis

Demographic data and responses to questions involving single categorical choices were reported as raw percentages. Questions based upon 5-point Likert scales were assumed to represent continuous scales and were thus reported as a mean response±standard deviation (SD); those questions bounded by Never (0 per cent) to Always (100 per cent) were reported as mean response as percentages±SD. One-sample *t*-tests with a midpoint of 3.00 (ie 'Neutral') were used to statistically test Likert-scaled questions that were bounded by Very Unimportant to Very Important and Strongly Disagree to Strongly Agree; a midpoint of 50 per cent (ie 'Sometimes') was used to test questions bounded by Never (0 per cent) to Always (100 per cent). Paired *t*-tests were used to ascertain statistical differences between responses from early- versus late-clinical phase trials. An alpha level of 0.05 was chosen *a priori* as the level of statistical significance. A comparison of firms that primarily utilised capital/securities markets was also conducted concerning the use of various financial tools for decision making prior to FDA approval. All data were entered electronically and all analyses were performed using SPSS version 14.0 (Chicago, IL) software for Windows®.

RESULTS

Demographics and general statements concerning R&D

Overall, only 29 usable surveys were returned, and seven firms stated that CFOs could not respond due to the confidentiality required for competitive strategy. No surveys were returned as undeliverable. Thus, a 7.5 per cent response rate was achieved (ie 29/389). Of those responding, approximately half (52 per cent) of companies were characterised as having year-end firm capitalised financial valuations of less than US$100m, spending under US$25m on R&D per year, and having fewer than 20 research scientists actively involved in R&D. Table 1 presents the demographics of the respondent firms.

Regarding general statements of R&D, respondents perceived that governmental policymakers did not understand the risk and uncertainty of drug development (mean response = 2.54±0.99 to the statement 'Governmental policymakers (eg regulators, politicians, legislators) understand the risk and uncertainty of drug development', $p < 0.025$). A neutral view was expressed concerning the

understanding of healthcare organisations regarding the value obtained from therapeutic agents (mean response = 3.38±1.17 to the statement that 'Healthcare organizations understand the value provided from pharmaceutical or biotechnology agents', $p < 0.131$). Consensus among respondents was observed on the importance of intellectual property to companies (all responses = 5.00 to the statement 'Intellectual property is an important asset to my firm').

Factors considered during early- versus late-clinical phase trials

Table 2 presents the responses concerning various factors (ie regulatory requirements, capital requirements, formulary adoption, investor expectations, and competitor activity) considered during early clinical phase trials (ie phase Ia, Ib, and IIa) and late clinical phase trials (ie phase IIb and III). With the exception of formulary adoption in early clinical phase trials, respondents indicated a significant importance to all the factors addressed ($p < 0.001$). An increasing importance from early- to late-phase clinical was noted for formulary adoption (paired mean score change = 1.21±1.02, $p < 0.001$), competitor activity (paired mean score change = 0.40±0.82, $p = 0.022$), and projected peak sales (paired mean score change = 0.36±0.64, $p = 0.009$). Regulatory requirements, capital requirements, and investor expectations remained important throughout early- and late-clinical phase trials (all scores >3.00, $p < 0.001$). In a separate question relating to investor expectations, achieving the required cost of capital was reported to be important for firm operations (mean response = 4.46±0.71 to the statement 'Achieving the required cost of capital is an important aspect of my firm's operations', $p < 0.001$).

Table 1: Firm characteristics of respondents

	Per cent responding (%)
Year-end market capitalisation	
<$100m	69
$100–500m	21
$501–1000m	7
>$1000m	3
Annual R&D expenditures	
<$25m	76
$25–250m	21
Number of research scientists actively engaged in R&D	
<20	62
20–50	14
51–100	21
>100	3
Number of firms	29

Funding for drug development and venture capital

Presented in Table 3, the rank-order sources utilised for funding of drug development were: venture capital >capital/securities markets >strategic alliances >federal government >company sales revenue.

Table 2: Importance of factors during early- versus late-clinical phase trials

	Early-phase importance* (ie, phase Ia, Ib, and IIa) [mean response (SD)]	Late-phase importance* (ie, phase IIb and III) [mean response (SD)]	Paired difference from early to late phase** [mean score change (SD)]
Factor			
Regulatory requirements	4.46 (±0.65)†	4.64 (±0.49)†	+0.20 (±0.58)
Capital requirements	4.46 (±0.86)†	4.54 (±0.54)†	+0.20 (±0.82)
Investor expectations	4.42 (±0.64)†	4.46 (±0.64)†	+0.08 (±0.57)
Projected peak sales	4.00 (±0.80)†	4.29 (±0.76)†	+0.36 (±0.64)‡
Competitor activity	3.88 (±0.59)†	4.21 (±0.57)†	+0.40 (±0.82)§
Formulary adoption	3.19 (±0.98)†	4.30 (±0.61)†	+1.21 (±1.02)†

*5-point Likert scale for each factor within groups: 'Very Unimportant'=1 to 'Very Important'=5.

**Between group significance (ie, early- versus late-clinical trial phase responses); paired t-test.

†Significant difference at the p < 0.001 level via one-sample t-test [midpoint: 'Neutral'=3.00] or paired t-test, as appropriate.

‡Significant difference at the p < 0.01 level via one-sample t-test [midpoint: 'Neutral'=3.00] or paired t-test, as appropriate.

§Significant difference at the P < 0.05 level via one-sample t-test [midpoint: 'Neutral'=3.00] or paired t-test, as appropriate.

Table 3: Funding source used for drug development

	Extent used (%)*[mean, per cent (±SD)]
Funding source	
Venture capital	67 (±42)**
Capital/securities markets	60 (±45)
Strategic alliances	52 (±30)
Federal government	20 (±26)†
Sales	14 (±26)†

*5-point Likert Scale: 'Never'=0% to 'Always'=100%.

**Significant difference at the $p<0.05$ level via a one-sample t-test [midpoint: 'Sometimes'=50%].

†Significant difference at the $p<0.001$ level via a one-sample t-test [midpoint: 'Sometimes'=50%].

Table 4: Use of analytic tools prior to FDA approval

	Extent used (%)* [mean, per cent (±SD)]
Analytic tool:	
Past experience/intuition/human judgment	85 (±21)**
Net present value (NPV)	74 (±24)**
Internal rate of return (IRR)	62 (±29)†
Decision analysis	59 (±30)
Sensitivity analysis	54 (±29)
Payback period/Discounted payback period	45 (±29)
Real options	28 (±36)†
Accounting rate of return	27 (±31)†
Economic value-added (EVA®)	22 (±26)**

*5-point Likert Scale: 'Never'=0% to 'Always'=10%.

**Significant difference at the $p<0.001$ level via a one-sample t-test [midpoint: 'Sometimes'=50%].

†Significant difference at the $p<0.01$ level via a one-sample t-test [midpoint: 'Sometimes'=50%].

‡Significant difference at the $p<0.05$ level via a one-sample t-test [midpoint: 'Sometimes'=50%].

Approximately one-quarter (24 per cent) of firms did not always (ie 100 per cent) rely upon venture capital or capital/securities markets. Notably, firms spending under US$25m on R&D per year were less likely to rely upon capital/securities markets for funding of R&D ($p<0.001$).

Of firms that were privately held and mailed an extended survey concerning venture capital ($n=19$), almost half (47 per cent) used at least three venture capital firms during the initial start-up, with the average number of venture capital companies being 2.2±1.8. Venture capital was reported as being most important during the preclinical phase (65 per cent), progressing through Phase I (6 per cent), Phase II (18 per cent), and Phase III (12 per cent). Disagreement was observed concerning any potential involvement that venture capital companies may have in the direct management of the firm (mean response = 1.80±1.01 to the statement that 'Venture capital companies should be involved with the direct management of the firm', $p<0.001$), although there was agreement that contacts extending from venture capital companies should be used for assistance with R&D (mean response = 3.95±0.69 to the statement that 'Contacts stemming from a venture capital company should be used for assistance with pharmaceutical or biotechnology R&D', $p<0.001$). Firms neutrally viewed a role for performance benchmarks within venture capital contracts (mean response = 3.35±0.99 to the statement 'Performance benchmarks (eg targets, deadlines) should be present within the contractual relationship between venture capital companies and pharmaceutical or biotechnology firms', $p<0.130$)

Analytic tools used in pre-approval decision making

The use of formal and informal analytic tools used within firms for decision making prior to FDA approval appears in Table 4. The three most commonly utilised techniques included past experience/intuition/human judgment (85±21 per cent), followed by NPV (74±24 per cent), and IRR (62±29 per cent). Approximately half of companies (48 per cent) always (ie 100 per cent) used at least one formal method other than past experience/intuition/human judgment. Furthermore, almost all companies (90 per cent) used at least one formal method at least 75 per cent of the time. Notably, firms relying upon capital/securities markets for funding of R&D a majority of the time were more likely to utilise past experience/intuition/human judgment as an analytic tool ($p=0.038$).

Use and application of pharmacoeconomics

The use and application of pharmacoeconomics by respondent firms

Table 5: Use and application of pharmacoeconomics

	Extent used (%)* [Mean, Per cent (±SD)]
Percentage of drug candidates that underwent any formal pharmacoeconomic evaluation	66 (±31)**
R&D or marketing component where pharmacoeconomics was applied	
Post-approval pricing and reimbursement	83 (±31)†
Pre-approval pricing and reimbursement	77 (±32)†
Licensing	72 (±27)‡
Go/No-Go decisions during clinical trials	64 (±45)
Initial pipeline decisions	55 (±27)
	Per cent reporting (%)
Single phase that pharmacoeconomics was first considered	
Pre-clinical	33
Phase I	22
Phase II	19
Phase III	26
Phase IV/Post-FDA approval	0
Single most common expertise used to conduct pharmacoeconomic evaluations	
In-house/Internal departments	57
Contract research organisations (CRO)	39
Academic institutions/Universities	4

*5-point Likert Scale: 'Never'=0% to 'Always'=100%.

**Significant difference at the $p<0.05$ level via a one-sample t-test [midpoint: 'Sometimes'=50%].

†Significant difference at the $p<0.001$ level via a one-sample t-test [midpoint: 'Sometimes'=50%].

‡Significant difference at the at the $p<0.01$ level via a one-sample t-test [midpoint: 'Sometimes'=50%].

appears in Table 5. Almost all companies (97 per cent) reported the use of pharmacoeconomics at any stage of R&D, with 66±31 per cent of drug candidates undergoing formal pharmacoeconomic analyses. Pharmacoeconomics was most frequently applied for components of pre- or post-approval pricing and reimbursement, followed by licensing, go/no-go decisions during clinical trials, and initial pipeline decisions. Pharmacoeconomics was always (ie 100 per cent) employed for any of these aforementioned components within 72 per cent of firms. The methodology was first considered by 55 per cent of firms before clinical trials or during Phase I. No firms reported that pharmacoeconomic analyses were first considered at the Phase IV/Post-FDA approval stage. Pharmacoeconomic evaluations were conducted primarily using the expertise of in-house/internal departments followed by contract research organisations; academic institutions/universities were rarely used as a primary source.

DISCUSSION

This research assessed several issues and various analytic methods surrounding the pipeline management of drug candidates within the biotechnology sector. Four specific areas were of focus: (1) factors considered during clinical trials; (2) sources of funding for R&D (including venture capital within privately held firms); (3) analytic tools used for decision making; and (4) the use and application of pharmacoeconomics.

Respondent firms may generally be categorised as small biotechnology companies valued under US$100m and spending less than US$25m on R&D per year. A relatively low response rate of 7.5 per cent was noted in the current study, with 29 completed survey instruments returned. Despite this, the response rate is similar to other academic studies targeting CFOs (eg Graham and Harvey[23] = 8.8 per cent, Trahan and Gitman[24] = 12.0 per cent, Ryan and Ryan[25] = 20.5 per cent). The broad Financial Executives Institute/Duke University quarterly survey of over 14,000 members and 8,000 firms also reported typical response rates of 8–10 per cent for high-level corporate policymakers such as CFOs.[23]

As previously addressed, the October 2006 US Congressional Budget Office report on R&D in the pharmaceutical industry highlighted the risk, uncertainty, and return associated with drug development.[3] Some of the primary determinants of R&D costs discussed in the report included the increasing length of time of preclinical and clinical phase trial research, the increasing number of investigational new drugs that fail during clinical phase trials, and the overall opportunity costs considering increasing R&D costs *vis-à-vis* expected sales revenue.[3] Results of the current study paralleled the importance of regulatory requirements, capital requirements, and investor expectations

throughout early- and late-clinical phase trials. Respondents, however, generally disagreed with governmental policymakers' understanding of the risk and uncertainty of drug development. Considerations of competitor activity, formulary adoption, and projected sales revenue emerged primarily as drug candidates approached FDA approval. Intellectual property was viewed as very important to firms by consensus, an issue addressed by Grabowski *et al.*[26] as being of long-term importance for follow-on biologics that may be developed to extend patent lives of products nearing the end of their patent lives.

Although the sources of leveraging capital for R&D efforts within respondent firms predominantly involved venture capital or capital/securities markets, strategic alliances also contributed an important role. Addressing some challenges of securing funding via venture capital, Pisano[27] noted that the investment time-frame of most venture capitalists is typically three years, remarkably less than the near 15-year time horizon required to bring a new drug to market. An analysis conducted by the National Venture Capital Association also reported that venture capital firms invested an average of US$3m per biotechnology company, with maximum amounts averaging US$20m – substantially less than the US$800m in capitalised monies needed on average to bring a new drug to market.[6,27] While both McCutchen and Swamidass[8] (1996) and Tyebjee and Hardin[4] (2004) addressed general leveraging strategies for biotechnology companies, McCutchen and Swamidass[28] and Danzon *et al.*[29] focused upon strategic alliances within the biotechnology and pharmaceutical sectors. Within the current study, funding from federal sources constituted a small role within respondent firms, even though the broader impact of declining monies from government sources was explicitly addressed within the 2006 Congressional Budget Office report on pharmaceutical R&D as potentially fuelling increases in future corporate R&D expenditures.[3] Finally, although the current study indicated that sales revenue did not contribute substantially to capital sources for R&D (perhaps due to the potentially small number of marketed products the firms had with which to generate sales), numerous authors have observed a strong link between sales revenue or internal funds and R&D among large firms (eg Bound *et al.*[30], Grabowski and Vernon[31]).

In attracting capital to fund R&D, firm and project valuations for many biotechnology companies often rely strongly upon intangible assets associated with R&D efforts rather than upon realised sales from approved and marketed products.[27] Skrepnek[9] addressed the lack of standardisation that exists in the valuation of intangible assets particularly within the pharmaceutical sector, also highlighting a need for more valid and robust *ex ante* and *ex post* techniques. With the numerous uncertainties associated with the progression of an investigational new drug through clinical trials, Pisano[27], however, noted that 'even the most sophisticated valuation techniques… are of limited use'.[14] Importantly, although DCF methods are viewed as being the foundation of pre-eminent capital budgeting tools, the operationalisation of these principles through advanced decision science methods should seek to appropriately address the specific and complex multifaceted nature and risk of associated with managing pipeline drug candidates. As stated by Bonabeau[12], however, 'when combined with experience, insight, and analytic skills of a good management team, (new decision support tools such as decision trees and real options) offer companies a way to make consistently sound and rational choices even in the face of bewildering complexity – a capability that intuition will never match'.

Concerning the specific valuation of investment opportunities, the current state of capital budgeting techniques used by corporations represents a shift since research published during the 1960s. For example, Istvan[32] found that the accounting rate of return (which is not based upon DCF principles) was viewed as the most popular capital budgeting technique, with methods based upon DCF principles (eg NPV) being the least. Currently, more robust methods based upon DCF methodologies appear to be favoured by firms, which more closely parallels sound financial theory; accounting

rates of return are now often viewed as the least favourable.[9,23,25,33,34] Results from the current study support that robust tools such as the NPV and IRR were used 74 and 62 per cent of the time, respectively. Although this general observation follows findings from other research (eg Graham and Harvey[23] reported that approximately 75 per cent of CFOs always or almost always use NPV or IRR), the CMR International report[13] of 28 drug firms indicated that financial models were considered of great benefit or essential only 11 per cent of the time to start preclinical research and 46 per cent to begin full-scale development.[25,33]

Relating to the other formal capital budgeting techniques investigated, Sharpe and Keelin[16] described the use of decision trees/ decision analysis within a three-stage process to evaluate new product portfolios at SmithKline Beecham, while Stonebraker[35] discussed their role in the management of biotechnology pipelines at Bayer. The current study reported that decision analysis was used 59 per cent of the time, while the CMR International (1997)[13] marketing report of the drug sector indicated that the technique considered 4 per cent of the time to start preclinical research and 29 per cent to begin full-scale development. The use of sensitivity analysis in the current study closely corresponds to the findings by Graham and Harvey,[23] being used 54 versus 52 per cent, respectively. Ryan and Ryan[25] reported that the sensitivity analysis was the most commonly used technique. The application of real options, although perhaps important for biotechnology R&D, was small and similar to accounting rates of return and EVA®. Graham and Harvey[23] reported that approximately 25 per cent of CFOs always or almost always use real options analysis relative to the 28 per cent use within the current study.

Despite the assessment of the aforementioned formal methods for making pipeline decisions, one of the more interesting findings involves the use of past experience/ intuition/human judgment 85 per cent of the time. In this context, an increasing scientific literature has addressed the role of intuition within decision making.[36,37] Although informal approaches such as human judgment have been recognised within the decision sciences, Bonabeau[12] strongly cautioned against intuition due to its inherent unreliability within complicated decision making as 'the more options you have to evaluate, the more data you have to weigh, and the more unprecedented the challenges you have to face, the less you should rely on instinct and the more on reason and analysis'. Bonabeau[12] also made reference to a 2002 executive survey which reported that 45 per cent of executives utilised instinct rather than empirics when managing business operations. Within the pharmaceutical industry, the CMR International[13] marketing report also noted that human judgment was the single most popular method compared to all other techniques. The CMR International[13] report found that human judgment exceeded all other methods by 47 or more percentage points when considering whether to start preclinical research, and 11 or more percentage points regarding full-scale development. Although not investigated in the current study, the rationale behind the use of informal methods extends to the investigation of loss functions within formal decision theory (ie methods for assessing economic losses or costs associated with comparative decision making between projects), whose role ultimately serves to unify estimation, prediction, hypothesis testing, and final policy recommendations.[37]

The role of pharmacoeconomics within healthcare has historically been to augment evidence-based approaches to care, to guide pricing decisions, or to aid in reimbursement for pharmaceuticals.[19,20,38] Thus, the application of pharmacoeconomics within R&D remains a relatively new practice. Within the current study, pharmacoeconomics was utilised during all phases of clinical trials and was applied for reasons beyond pricing and reimbursement. Formal pharmacoeconomic evaluations were considered for 66 per cent of drug candidates. Comparatively, health economics data were considered of great benefit or essential within the CMR International[13] report among 14 per cent of respondents to start preclinical research and 46 per cent to begin full-scale development. In an investigation of 31 drug

companies, DiMasi *et al.*[19] reported that pharmacoeconomics was occasionally, frequently, or always used for licensing among 71 per cent of respondents, for go/no-go among 68 per cent, and for pipeline among 73 per cent; each of these figures decreased to 50 per cent for all categories within small companies. Noting that the predominant use of pharmacoeconomics in the current study was for pricing and reimbursement (ie pre-approval use = 77 per cent, post-approval use = 83 per cent), the methodology was reportedly used for licensing, go/no-go, and initial pipeline decisions 72, 64, and 55 per cent of the time, respectively. DiMasi *et al.*[19] also noted that the primary use of pharmacoeconomics was to support pricing and reimbursement, with 89 per cent of respondents using the methodology for such purposes in the US.[19] Furthermore, almost three-quarters (73 per cent) indicated an expected increase of pharmacoeconomics.[19] From the perspective of healthcare providers, Motheral *et al.*[39] reported that pharmacoeconomics was helpful or somewhat helpful among 88 per cent of respondents that were employed within managed care organisations. While DiMasi *et al.*[19] found that pharmacoeconomics was integrated into studies during Phase I, II, III, and Post-Approval 15, 29, 71, and 71 per cent, respectively, the current study found that pharmacoeconomics was first considered during the preclinical stage or Phase I 55 per cent of the time.[19] Importantly, no firms in the current study waited until post-approval to first consider the methodology. Concerning the role of outsourcing, DiMasi *et al.*[19] noted that 72 per cent of small firms outsourced a majority of their pharmacoeconomics budget. The current investigation found that 39 per cent of respondents indicated that their primary source of pharmacoeconomics expertise was that of contract research organisations compared to in-house/internal departments and academics/universities being 57 and 4 per cent, respectively.

There are several limitations that should be considered when assessing the current research endeavour. Foremost, results may not necessarily be generalisable to the overall population that was investigated. Although the response rate was consistent with prior research of CFOs and senior-level executives, it remained relatively low. A nonresponse bias may also be present, wherein individuals who did not complete and return the survey instrument may systematically differ from those who did. Although the study was anonymous, some of the executives may have not been able to complete the survey due to corporate policy that precluded them from participating in external research regarding competitive strategic management. Despite these limitations, the overall policy implications of the current study are particularly relevant to companies involved in biotechnology or pharmaceutical R&D.

In a broad policy context, the long-term performance of the biotechnology sector was addressed in a *Harvard Business Review* paper titled 'Can Science Be a Business? Lessons from Biotech'. Therein, Pisano[27] stated that the biotechnology industry continues to be best categorised as an emerging sector that has not yet capitalised upon its full potential, even though over US$300bn has been leveraged since its genesis in the 1970s.[27] Overall, it was surmised that 'for biotechnology to fully succeed, its anatomy must help the players collectively to excel in three ways: managing risk and rewarding risk taking, integrating the skills and capabilities that reside in a range of disciplines and functions, and advancing critical knowledge at the organisational and industry levels'.[27] Thus, although a strong need exists for robust decision-making tools, these alone may be viewed as being a required, though insufficient, method in establishing sustainable competitive advantages and growth. Ultimately, numerous elements of leadership, management, finance, and decision science must be dynamically evaluated, implemented, and monitored by firms and executives. In this context, Hatfield *et al.*[40] reported in a working paper that companies that analysed all investment projects via formal DCF capital budgeting techniques (eg NPV, IRR) had higher average stock market share prices than those that did not, although the sole reliance upon NPV did not maximise returns across firms.

Future work involving the valuation and management of drug pipelines is both challenging and necessary to ensure the

optimisation of risk and return associated with innovation activity and to establish value for stakeholders. In advancing the use of decision sciences to evaluate R&D projects, case studies exemplifying the appropriate use of various methods should ultimately be conducted in conjunction with the continued development of novel models that may capture the multifaceted characteristics and uncertainties associated with the drug development process and final adoption or reimbursement decisions (eg Bayesian methods, iterative learning models).[38] To assure seamless transitions from clinical trials to real-world use, pharmacoeconomic analyses may also be considered to optimise utilisation practices and outcomes within healthcare systems. Ultimately, the development of robust techniques to manage pipeline portfolios becomes a requisite to establish a foundation for economic growth that may unify basic research, commercialisation, translational research, and clinical utilisation. Researchers and executives alike should seek to investigate the role between the use of various analytic methods and the final performance of firms.

CONCLUSION

Results of this investigation are reflective of the risk and uncertainty of R&D in the pharmaceutical and biotechnology sectors. Although the single most frequently cited decision-making technique used was prior experience/intuition/human judgment, methods based upon robust DCF approaches (ie NPV, IRR) were also used frequently. An increasing use of more formal methods of analysing drug pipeline portfolios may afford senior executives with an increased ability to make more informed decisions to better hedge risk and maximise return. Continued research is warranted to establish the role of robust techniques for decision-making with the management of drugs in the pipeline and with the overall financial performance of firms.

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