Vaccine 32 (2014) 3336–3340

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Toward more specific and transparent research and development costs: The case of seasonal influenza vaccines

Ayman Chit[a,*], Jayson Parker[a], Scott A. Halperin[b], Manny Papadimitropoulos[a,c], Murray Krahn[a], Paul Grootendorst[a]

[a] University of Toronto, Toronto, Ontario, Canada
[b] Canadian Center for Vaccinology, Dalhousie University, Halifax, Nova Scotia, Canada
[c] Eli Lilly Canada Inc., Scarborough, Ontario, Canada

ARTICLE INFO

Article history:
Received 29 September 2012
Received in revised form 21 May 2013
Accepted 19 June 2013
Available online 3 July 2013

Keywords:
Cost
Economics
Research and development
Influenza
Vaccine
Clinical trial
Risk
Biologic
Drug development

ABSTRACT

Background: The ability to calculate the development costs for specific medicines and vaccines is important to inform investments in innovation. Unfortunately, the literature is predominated by non-reproducible studies only measuring aggregate level drug research and development (R&D) costs. We describe methodology that improves the transparency and reproducibility of primary indication expected R&D expenditures.
Methods: We used publically accessible clinical trial data to investigate the fate of all seasonal influenza vaccine candidates that entered clinical development post year 2000. We calculated development times and probabilities of success for these candidates through the various phases of clinical development. Clinical trial cost data obtained from university based clinical researchers were used to estimate the costs of each phase of development. The cost of preclinical development was estimated using published literature.
Results: A vaccine candidate entering pre-clinical development in 2011 would be expected to achieve licensure in 2022; all costs are reported in 2022 Canadian dollars (CAD). After applying a 9% cost of capital, the capitalized total R&D expenditure amounts to $474.88 million CAD.
Conclusion: Clinical development costs for vaccines and drugs can be estimated with increased specificity and transparency using public sources of data. The robustness of these estimates will only increase over time due to public disclosure incentives first introduced in the late 1990s. However, preclinical development costs remain difficult to estimate from public data.

1. Introduction

There has been polarizing debate in the literature regarding the "true" cost of developing new pharmaceutical drugs. In a much-publicized paper, DiMasi and colleagues estimate the cost of developing a new molecular entity (NME) in 2001 to be in the order of $800 million United States dollars (USD) [1]. More recently, Paul and colleagues estimated the cost to be in the order of $1.8 billion USD [2]. Critics suggest that these estimates are vastly overstated. Donald Light and Rebecca Warburton estimate the cost of new drug development to be well under $100 million USD [3]. One reason for the controversy is that most cost-of-research and development (R&D) studies are not reproducible. Morgan and colleagues, in a recent review article, note that 10 of the 13 cost-of-R&D studies in the literature were based on self-reported, unaudited and confidential data from unnamed drug companies and unnamed products [4]. The non-reproducible aspect of these data raises questions about the representativeness of the R&D cost estimates. Critics also question the value of estimating average drug R&D costs given the substantial heterogeneity in development costs within a therapeutic area. For instance, Adams and Brantner report that the expected cost of developing an oncology medicine is $1.042 billion USD while the cost of developing a medicine within this class–drugs that treat breast cancer – is $0.61 billion USD [5]. The narrowly defined R&D cost in this case would be more informative for decision making around new investments in breast cancer drugs.

In this paper, we use publicly available data to estimate the cost of development of seasonal influenza vaccines if the development was all conducted in Canada. In contrast to most other studies, our analysis is reproducible and narrowly defined to a therapeutic area. Although our primary contribution is methodological, we note that

* Corresponding author at: Leslie Dan Faculty of Pharmacy, University of Toronto, 144 College Street, Room 601, Toronto, ON, M5S 3M2, Canada. Tel.: +1 416 587 4651.
E-mail address: Ayman.Chit@utoronto.ca (A. Chit).

0264-410X/$ – see front matter.
http://dx.doi.org/10.1016/j.vaccine.2013.06.055

estimation of seasonal influenza vaccine R&D costs is of interest in its own right. Relative to drugs, estimates of vaccine development costs are limited. Moreover, influenza continues to impose a substantial burden of morbidity and mortality. Influenza vaccines are amongst the most effective means of protection against influenza infection, for instance current vaccines can prevent up to 62.1% of influenza related respiratory hospitalization [6]. Despite this, the US Centers for Disease Control estimates that the annual epidemic burden of seasonal influenza in the United States is $87.1 billion USD (C.I., $47.2, $149.5) [7]. Given the residual high burden of disease improved influenza vaccines are a high development priority, and many are currently in development [8].

2. Methods

2.1. Model and data sources

The total, expected, uncapitalized, R&D cost C_u required to bring a vaccine candidate (VC) to market is the sum of expected uncapitalized R&D expenditures during the pre-clinical phase C_p and the clinical phase C_c.

$$C_u = C_p + C_c$$

Following the methods developed by DiMasi [9], the expected clinical phase cost per approved vaccine, C_c, is defined as

$$C_c = \frac{E(h)}{S}$$

s is the probability that a VC emerging from pre-clinical development obtains market approval. $E(h)$ is the expected value of the clinical period costs (h) and can be defined as:

$$E(h) = p_I\mu_I + p_{II}\mu_{II} + p_{III}\mu_{III} + p_A\mu_A$$

p_I, p_{II} and p_{III} are the probabilities that a VC tested in humans will enter phase I, II and III, respectively, p_A is the probability that long-term animal testing will be carried out. μ_I, μ_{II}, μ_{III} and μ_A are mean costs of developing a VC in phases I, II, III and long-term animal testing, respectively.

Firms are generally not able to allocate all pre-clinical costs to specific VCs. We were not able to identify reliable publicly available sources of information to directly estimate C_p. DiMasi reported a general ratio of pre-clinical expenditures to total R&D expenditures, λ, of 30% [9]. We used this same estimate to calculate C_p using the following equation.

$$C_p = \left[\frac{\lambda}{1-\lambda}\right] C_u$$

We adjusted our cost estimates to account for the cost of capital using methods previously described by DiMasi [9]. Harrington and colleagues in a recent working paper have updated the cost of capital for the pharmaceutical sector and estimate it to be 9% [10]. DiMasi in previous work estimated an 11% cost of capital [11]. Given the controversy around which rate to use, we employed 9% in this study and conducted sensitivity analysis using 5% and 11%. The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends a 5% discount rate be used in health technology appraisals [12]. Light et al. propose this rate as a substitute for market derived cost of capital rates [13].

Our model does not account for R&D tax incentives that are traditionally offered by the Canadian government to developers. The Canadian Scientific Research and Experimental Development (SR&ED) tax incentive program is used to reduce corporate tax owed on revenue [14]. Thus, while private corporations are rewarded through tax payer subsidies for engaging in R&D, the actual cost of developing the drugs remain the same.

In this study we used *Trialtrove*, a database held by Citeline intelligence solutions. This data base is primarily built on data from clinicaltrials.gov and is supplemented through routine mining of a broad range public domain sources [15].

Further, this approach allows us to exploit the disclosure mandates on human research that were first promulgated in 1997 by the US Food and Drug Administration Modernization Act, and which were bolstered by the 2004 decision by the International Committee of Medical Journal Editors to not publish results of clinical trials that had previously not been publicly registered [16]. The result is that a drug company cannot seek FDA approval for a new drug nor can it publish the results of its clinical trials in a reputable journal without having previously disclosed their clinical research. The new requirements have led to the public disclosure of clinical research programs, including sponsorship, the identity of the investigational product and study design (phase, number of subjects, length of study, number of centers, primary endpoints, etc.). These data allow us to avoid selection biases that may have contaminated other cost of R&D studies, while also providing information on the quantity of the "inputs" used to conduct the R&D – the number of subjects, the number of measurements per subject, study duration, etc. These data are silent, however, on the unit costs of these inputs. For that, we obtained cost estimates from a well-known influenza research group in Canada known as the Canadian Center for Vaccinology (CCfV), at Dalhousie University in Halifax, Nova Scotia, Canada [17]. CCfV is a member site of the Public Health Agency of Canada/Canadian Institutes of Health Research Influenza Research Network (PCIRN) [18]. Cost data were provided in Canadian Dollars which has been close to parity with the U.S. Dollar since 2007. No confidentiality agreements were required for this collaboration.

2.2. Estimating model parameters

We collected all the clinical trial records on seasonal influenza VCs that entered clinical development after the year 2000 until 2011. For each trial record we extracted information on the study design, a description of the underlying biotechnology, the name of the sponsor, the study phase (I, II, III), number of subjects enrolled, study start and end dates, as well as the most recent public reports on product development status. We organized the data to track the VCs' development path. Once a VC entered a clinical development phase j (j could be phase I, II or III), it could either successfully transition to phase $j+1$ or to regulatory submission if it was already in phase j = III. Alternatively, the VC could be abandoned during development. The mean length of phase j was calculated by subtracting the start date of phase j from the start date of phase $j+1$ for the VCs that successfully made a transition. Any VC that did not transition to phase $j+1$ after being in phase j for longer than the upper bound of the 95% CI of the mean length of phase j were considered abandoned. VCs in phase j that did not transition to phase $j+1$ and had development times lower than the upper bound of the 95% CI of the mean phase j length were considered right censored. In this manner our data set was organized as time to event data (abandonment or successful transition) that includes censored observations. The time to event data set is included in Appendix I. These data were used to estimate p_j, the probability over development time t, that a VC will enter phase j of testing given that the previous phase was entered.

To estimate p_j we calculated the cumulative incidence (CI) function for successfully transitioning from phase $j-1$ to j of development [19]. This function estimates the probability that a VC transitions from phase $j-1$ to j before time t and that this occurs before the competing risk of abandonment. The function utilizes the Kaplan–Meier estimator that accounts for censored observations. Appendix II summarizes how this approach works. To calculate s