THE OPTIMAL DEVELOPMENT AND EFFICIENT REGULATION OF HEALTH CARE TECHNOLOGIES

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Abstract

A recent review of UK health research funding in the UK proposes to reform biomedical research prioritisation and aspects of licensing and regulation for new pharmaceutical drugs. This reform aims to foster innovative pharmaceutical products and to ensure that basic research is translated into health and economic benefits.

We propose a framework to value drug products at early (pre-clinical) stages of development under conditions of uncertainty. We set a theoretical real options model with Bayesian updating to characterise accumulation of experimental knowledge for a commercial developer that takes the decision to invest in experimentation on behalf of society.

We then model drug licensing and reimbursement regulation and characterise the value of the new drug conditional on regulatory regimes. We use this model to characterise optimal conditions under which a new drug should be developed, optimal commercial experimentation decisions and their impact on societal utility. We then propose a framework to evaluate whether licensing and reimbursement regulation offer incentives to the commercial agent to deliver new drugs, and characterise societal overall gains and losses for each regulatory regime considered.

We illustrate some shortcomings of current regulation. We show that a pure licensing regime using a statistical test of hypothesis does not incentivise the provision of optimal societal information. However a reimbursement regime is associated with overall societal costs that may be reduced with reimbursement coverage or pricing decisions.

1. Introduction

A newly developed drug is subject to strict market licensing regulation which depends on experimental quantification of the drug's postulated benefits. The drug licensing process relies on a particular type of experimental information, i.e. a hypothesis test around some clinically relevant measure of health improvement measured in one or more , often randomised, clinical trials (RCT).[1] The uncertain nature of experimentation transmits to the outcomes of investing in a new drug, from the perspective of both the commercial private investor and society that shares an interest in development to enjoy the resulting benefits in health gain. Therefore the productivity of investing in drugs development research relies on the interaction between efficiency of research and efficiency of regulation within the broader framework of market demand for drugs.[2]

Licensing regulation, introduced in response to the Thalidomide case, has recently become the focus of criticism as it has performed poorly in several respects.

First, regulatory requirements involve high sunk development costs[3] therefore unsuccessful licensing implies a risk of large financial losses. The licensing process delays marketing of the new drug imposing large commercial[4] and societal opportunity costs.[5] Second, cases of licensed drugs later withdrawn due to unforeseen adverse events are rare yet recurrent despite approval regulation.[6] Growing criticism of the licensing regime have focused on its failure to ensure the provision of sufficient information around uncertain benefit and risks associated with new drugs, particularly around drug's safety.[5;7] Third, based on the decrease in the number of investigational NDA applications in the last 10 years[8], it is feared

that regulation has repercussions on the supply side both depleting development pipelines and adversely affecting innovation within the pharmaceutical industry[7;8] with no short-term societal benefits and longer term losses.[9] Forth, concerns are increasing around the deterioration of the business environment in some Countries where reimbursement regulation has been introduced (UK, Sweden, Australia Canada). Reimbursement regulation is based on cost-effectiveness information that synthesises the balance of gains and losses in effectiveness and quality of life associated with a drug, and as such it is the nearest, albeit arguably imperfect, form to assessing societal benefit from a drug. There are views that reimbursement regulation could cause major pharmaceutical companies to disinvest from some Countries, in particular the UK.

It has been suggested[7] that a more efficient mechanism to signal healthcare societal priorities to the pharmaceutical industry should provide indications around which drugs to develop and around which research could maximise the chances of the drug to pass regulatory hurdles. Such mechanism may mitigate some of the uncertainties around market success for new drugs. Yet, despite the high uncertainty surrounding decisions to develop new healthcare technologies, structured decision-making for go/no-go is rarely documented[10;11] and probably, rarely used in practice. Lack of practice implies the absence of a method to rationally take go/no-go decisions compatible with societal priorities.

We contribute to this debate developing a method to conduct structured decision-making in drugs development, based on economic incentives and incorporating uncertainty and current regulatory arrangements.

This paper is divided in two sections. In the first, we develop a drug development model incorporating commercial and societal rewards from developing a new drug and given current regulatory rules. We then describe conditions for optimal drugs development decisions. In the second section, we use this framework to explore incentives to conduct research implicit in current licensing regulation. A framework to vale the reimbursement regime is then outlined, and using proposed pricing reforms as an example, we provide an illustration of the potential interaction of different types of regulation and their impact on drugs development decisions.

2. A model of drugs development

We develop a Bayesian decision-theoretical[12] normative model of drug development choices based on the economic value of a drug under development. The model describes a specialised commercial agent's (commercial decision-maker) decisions to develop a drug (go) or not (stop) given current regulatory constraints. A go decision implies investment in experimentation, enacted by the commercial agent on behalf of society, and necessary to fulfil regulatory requirements.

Key drug development decisions are taken under uncertainty. Before development, the characteristics of the drug that will be observed during development and upon which the regulatory process relies, are unknown. However the commercial agent and society share prior information regarding them. Let $\Theta = \{q_1,...,q_n\}$ be the set of

prior beliefs and uncertainties held by each agent around all potential future observations of the characteristics of the drug. We assume that information is non-excludable and symmetric i.e. the set of uncertainties is common to either decision-maker and information accrues to either agent as soon as available. We also simplify the problem assuming that the drug is first on the market, its characteristics are measured relative to a placebo and no competitor drugs exist.

Let $A_c = \{a_0, a_1\}$ be the set of development actions of the commercial developer with $a_0 = stop, a_1 = go$, and $A_s = \{a_0, a_1\}$ the set of society's development options including any feasible actions in A_c, with $A = A_c \times A_s$ the set of combined commercial and societal development decisions. We interpret societal decisions as choices that society would take if decisions were not mediated by a commercial agent. In the remainder, the subscript 'c' and 's' indicate the commercial and societal agent. Let B_c and B_s be the set of all potential future benefit of the drug to each agent, dependent on Θ. The value of payoffs u_s, u_c is a utility function dependent on decisions and prior information $u_c = u_c(a_c; b_c(q))$, and $u_s = u_s(a_s, b_s(q))$. A rational commercial agent selects the development action that maximises her expected utility. Likewise, society prefers the action that maximises expected societal benefit.

The standard decision-theoretical approach above is vague in two respects fundamental in the context of drug development.
First, the description of benefits above assumes that benefit is accrued regardless of how uncertainties resolve. However, as regulatory rules are a necessary condition for accruing commercial or societal gains from the drug, the drugs development payoff must incorporate explicit regulatory decisions that depend on the observed characteristic of the drug, i.e. on resolution of uncertainty. The incorporation of this condition is illustrated in Section 2.1.1.

Second, we ignore the role of investment costs, assuming null development costs throughout. The characterisation of the action 'go' depends on sufficient conditions for drugs development decisions, including updating of information and the cost of information, i.e. the cost of development. Sufficient conditions are not examined in this paper.

2.1. Regulatory rules

We describe regulatory behaviour with an acceptance rule based on a test t dependent on q. Before development, regulatory outcomes are uncertain. Based on current information, each agent could only predict whether the 'average' parameter will fulfil the rule t.
This approach contrasts with the assumptions of rationality and full information of the commercial agent as it requires her to ignore the distribution of prior beliefs $q_1, ..., q_n$ associated with a probability of regulatory success. It also contrasts with rational and fully informed regulatory decisions, as they depend entirely on the observed characteristic of the drug $q_1, ..., q_n$, i.e. given a particular predicted realisation of

uncertainties. Therefore regulatory constraints can be incorporated in the value of the drug if regulatory decisions can be predicted conditionally on uncertainties being resolved, i.e. assuming that development yields perfect information.

Given a realised value $q_1,...,q_n$ and a test t, the acceptance rule takes the values $d(t,q)=\{d_0,d_1\}=\{0,1\}$, with probability n and $1-n$, and partitions the set of (commercial and societal) payoffs, B_c, B_s in two subsets $\{0, B_c|d_1\}, \{0, B_s|d_1\}$ conditional on perfect information.

Acceptance decisions do not belong to the set of 'stop' or 'go' decisions A, but are constraints to the accrual of payoffs as unlicensed drugs will not be made available for consumption.

2.1.1. License and reimbursement rules

We characterise two regulatory rules, licensing (subscript *l*) and combined licensing and reimbursement (subscript *r*). We simplify notation reducing the set of uncertainties to one parameter $\Theta=\{q\}$, i.e. an experimental measure of effectiveness with drug or placebo.

A license to market a drug must be supported by one or more Phase III clinical trials[1] comparing any one or more clinically meaningful measures[1] of health improvement with the new drug compared to alternative therapy or placebo. A drug is licensed when a frequentist statistical test of significance, generally at 95% confidence level is reported in the trial(s). We assume that licensing applications require one trial only and that a significant p-value implies successful licensing and listing of the drug in a dispensing formulary. The probability of licensing for a new drug is

$$n_l(t_l,q)=\int_{-\infty}^{+\infty} d_l(t_l,q)p(q)d(q) \qquad (1)$$

where $t_l: H_0: q_{tr}=q_{pl}$ is rejected at a = 0.05 significance level and q_{tr}, q_{pl} are a realisation of the effectiveness parameter.

A combined licensing and reimbursement rule reflects the practice of taking separate licensing and reimbursement decisions, as in some major drugs markets as the UK.[13] A licensed drug is reimbursed[2] if regarded as cost-effective, i.e. with positive net monetary benefit $lQ(q)-P$.[14] Such judgement depends on the cost-effectiveness threshold l that indicates the societal willingness to pay for one unit of

[1] In this setting we abstract from which of the numerous measures of health outcomes are used to support licensing applications, i.e. cure, deaths, adverse events, quality of life scores etc… See reference [1] for details.

[2] In all regulatory systems, reimbursement is conditional on successful licensing, i.e. a drug will not be reimbursed if not licensed. In this paper we will use the term 'reimbursement' as a short form for 'combined licensing and reimbursement ', unless otherwise stated. The term licensing should be interpreted as 'licensed for sale' i.e. marketing approval. This terminology is not unambiguous, as for example in the case of drugs used 'off patent' i.e. a drug licensed for a particular indication is also used for other conditions. In these cases, licensed should be interpreted as 'available on the market' as the drug is sold but not formally licensed for the particular off-patent use; explicit reimbursement decisions are currently restricted to licensed indications, hence cannot be taken for off-patent use.

health gain (Q) or the shadow price of the budget constraint for publicly funded health care, and the cost of the drug P (i.e. price).
The joint probability of licensing and reimbursement is

$$n_r(t_r,q)=\int_{-\infty}^{+\infty} d_r(t_r,q)p(q)d(q) \quad (2)$$

where $t_r = t_l \cap lQ(q) \geq P$.

The joint probability of licensing and reimbursement can be expressed as the product of the marginal probability of licensing and the conditional probability of reimbursement given licensing,

$$n_r(t_r,q)=\int_{-\infty}^{+\infty} d_l(t_l,q)d_{r|l}(t_{r|l},q)p(q)d(q) \quad (3)$$

and therefore $n_r(t_r,q) \leq n_l(t_l,q)$. Henceforth we omit $t_l, t_{r|l}$ from $n_r(q), n_l(q), d_l(q)$ and $d_{r|l}(q)$.

2.2. Payoffs from a new drug

We model the value of a licensed drug given a combination of market coverage and public reimbursement restrictions, with three relevant regimes:

- Demand-constrained licensing (*l*), with no reimbursement restrictions but budget-capping or other expenditure controls;
- Demand-constrained, permissive reimbursement (*r*) with reimbursement restrictions and expenditure controls;
- Unconstrained, mandatory reimbursement (*m*) with reimbursement restrictions but no expenditure control, e.g. total coverage a la NICE (UK National Institute for Health and Clinical Excellence).[13]

2.2.1. Coverage constraints

Drug sales are constrained by a linear, price-elastic inverse demand function

$$d = 1 - bP \text{ if } 0<b<1, \quad 0 \text{ elsewhere} \quad (4)$$

with *b* the market quota. For a population *N*, the total market size for the drug is *d*N* if a demand constraint applies, and *N* (d=1) otherwise.
This is a simplified demand function independent from the value of the drug to society, from demand of substitutes and from the effectiveness of the drug. Hence the demand constraint *d* should be interpreted as a coverage constraint but cannot be interpreted in terms of uncertainty in the value of commercial sales.

2.2.2. Commercial payoffs with regulatory and market constraints

The commercial agent values a new drug using Net Present Value (NPV), the discounted value of drug's sales, $B_c = NPV = PNd$ assuming no development cost. Conditional on regulation, the set of commercial payoffs is $B_{c|t} = \{PNd * d(q)\}$.

The expectation of conditional payoffs under licensing and given perfect information is simply the value of NPV by the probability of licensing

$$
\begin{aligned}
u_{c,l} = u_{c,q}|t \quad &= \int_{-\infty}^{+\infty} PNd * d(q)p(q)d(q) \\
&= \int_{-\infty}^{+\infty} PNd|(d(q)=1)p(q)d(q) \\
&= n_l(q) * PNd
\end{aligned}
\tag{5}
$$

as regulatory success is the only source of commercial uncertainty, given demand and price. This is not the general case but rather a simplifying assumption in our model.

Likewise, the NPV conditional on the probability of licensing and reimbursement given the coverage constraint is the value of NPV by the probability of reimbursement,

$$
\begin{aligned}
u_{c,q}|t_r \quad &= \quad u_{c,r} = \\
&= \quad n_l(q) * n_{r|l}(q) * PNd
\end{aligned}
\tag{6}
$$

and, omitting the demand constraint for the mandatory reimbursement regime,

$$
\begin{aligned}
u_{c,m} \quad &= \quad d^{-1}u_{c,r} = \\
&= \quad n_l(q) * n_{r|l}(q) * PN
\end{aligned}
\tag{7}
$$

2.2.3. Societal payoff with regulatory and market constraints

The societal valuation function is a measure of the marginal monetary gain of an improvement in health status i.e. the consumer's net benefit from the drug[14] $B_s = lQ(q) - P$ (as in Section 2.1.1 above). The societal payoff conditional on regulation is $d(lQ(q) - P)d(q)$.

The total expected societal payoff conditional on licensing is

$$
\begin{aligned}
u_{s,q}|t_l \quad &= \quad u_{s,l} \\
&= \quad dN \int_{-\infty}^{+\infty} (lQ(q) - P)d_l(q)p(q)d(q)
\end{aligned}
\tag{8}
$$

and conditional on permissive reimbursement,

$$
\begin{aligned}
u_{s,q}|t_r \quad &= \quad u_{s,r} \\
&= \quad dN \int_{-\infty}^{+\infty} (lQ(q) - P)d_l d_{r|l}(q)p(q)d(q)
\end{aligned}
\tag{9}
$$

and $d^{-1}u_{s,r}$ under mandatory reimbursement, omitting the demand factor as before.

These values differ from commercial conditional payoffs in two respects. First, the probability of licensing conditions the distribution of $lQ(q) - P$ therefore it can be considered as a 'given'. However, unlike (unconditional) commercial sales, (unconditional) net benefit is uncertain, hence whilst the marginal distribution of commercial revenue is independent from Θ (as in (6) and (7) in Section 2.2 above), the marginal distribution of net benefit is not.

Second, under reimbursement, the value of the payoff and the regulatory decision are such that $d_{r|l} = d\left(lQ(q) > P \middle| d_l = 1 \cap d_r = 1\right) = 1$. The conditional distribution of societal payoffs is always non-negative, reflecting the reimbursement condition (NB>0) imposing a lower non-negative bound to the value of the drug.

3. Optimal drugs development decisions

We describe the necessary conditions for a 'go' commercial or societal decision, initially assuming no cost of development. The sufficient condition for a 'go' decision including updating of information and the cost of investment will be illustrated elsewhere.

3.1. Commercial development decisions

The commercial agent selects from the action set $A_c = \{a_0, a_1\}$ the action $a_0 = stop$ or $a_1 = go$ which maximises the expected NPV of the drug (Section 2.2), $a_c : u_{c,q}\middle|t, a_c = \max_{a_c}(0, u_{c,q}\middle|t)$. Therefore, development is chosen if $u_{c,q}\middle|t, a > 0$.

Under licensing, the value of the drug $u_{c,l} = n_l(q) * PNd$ is always positive because of $n_l(q) \neq 0$ always. Therefore, the necessary condition for a commercial agent to develop a drug under licensing is always satisfied if costs are null.

Under permissive reimbursement, the commercial DM will take a go decision if the probability of reimbursement is positive and if the expected revenue is positive, $u_{c,r}\middle|a = \max\left(0, n_l(q) * n_{r|l}(q) * PNd\right)$. A commercial 'go' decision requires the conditional probability of reimbursement given licensing, $n_{r|l}(q)$ to be non-null. Therefore under reimbursement there exists a cost-effectiveness threshold k_r^c where $lQ(q) > P$ at which the commercial DM will develop.

The value of the drug conditional on regulation and stop and go threshold for the commercial agent are illustrated in Figure 1.

As decisions are independent from the coverage parameter *d*, there is no difference between optimal commercial decisions with mandatory and with permissive reimbursement.

3.2. Societal drug development preferences

The societal decision maker prefers the action a_s in $A_s = \{a_0, a_1\}$ that maximises the payoff $u_{s,q}\middle|t$ (Section 2.2.3), $a_s : u_{s,q}\middle|t, a_s = \max_{a_s}(0, u_{s,q}\middle|t)$. Given a threshold $k_t = k(q, t, l)$ that partitions the values of $u_s\middle|t$ such that $u_s\middle|(t, l < k_t) \leq 0$ and $u_s\middle|(t, l > k_t) > 0$, go decision taken if society is willing to pay at least $l > k_t$ for a unit of health gain.

Under licensing, the societal net benefit from the drug is equal to the probability of licensing multiplied by the value of the drug conditional on licensing being fulfilled,

$$\begin{aligned} u_{s,l} &= n_l(q) * (u_s | d_l = 1) = \\ &= \int_{-\infty}^{+\infty} dN\,(lQ(q) - P) d_l(q)\, p(q)\, d(q) \end{aligned} \tag{10}$$

with $n_l(q) > 0$ always. The societal 'go' threshold k_l is identified studying the condition under which $u_{s,l}$ is positive. First, the expected value of the drug can be partitioned with respect to Θ such that

$$(u_{s,l} | d_l = 1) = \int_{lQ(q)>P} (lQ(q) - P) d_{r|l}(q)\, d(q) + \int_{lQ(q)\leq P} (lQ(q) - P) d_{r|l}(q)\, d(q) \tag{11}$$

and as the two terms in (11) are conditional distributions, it is possible to rewrite the value of the drug under licensing as

$$u_{s,l} = n_l(q) * n_{r|l}(q) R^+ + n_l(q) * (1 - n_{r|l}(q)) R^- \tag{12}$$

where R^+, R^- have an immediate economic interpretation, respectively the conditional expectation of opportunity gains and opportunity losses from development. The sign of $u_{s,l}$ depends on the balance of R^+, R^-. A 'stop' decision is taken if $u_s | (d_l = 1) \leq 0$ in which case it must be $\frac{R^+}{|R^-|} > \frac{1}{n_{r|l}(q)} - 1$. The term R^- indicates that with licensing, potential negative net benefits could still be realised once the drug is developed since NB can be negative although positive on average. This balance is a function of the distribution of uncertainties Θ and on l, therefore the value of the drug becomes positive as lambda increases.

As for the commercial decisions, societal decisions are independent from coverage therefore are the same for permissive or mandatory reimbursement. Hence we will ignore the term *dN* in the rest of this section.

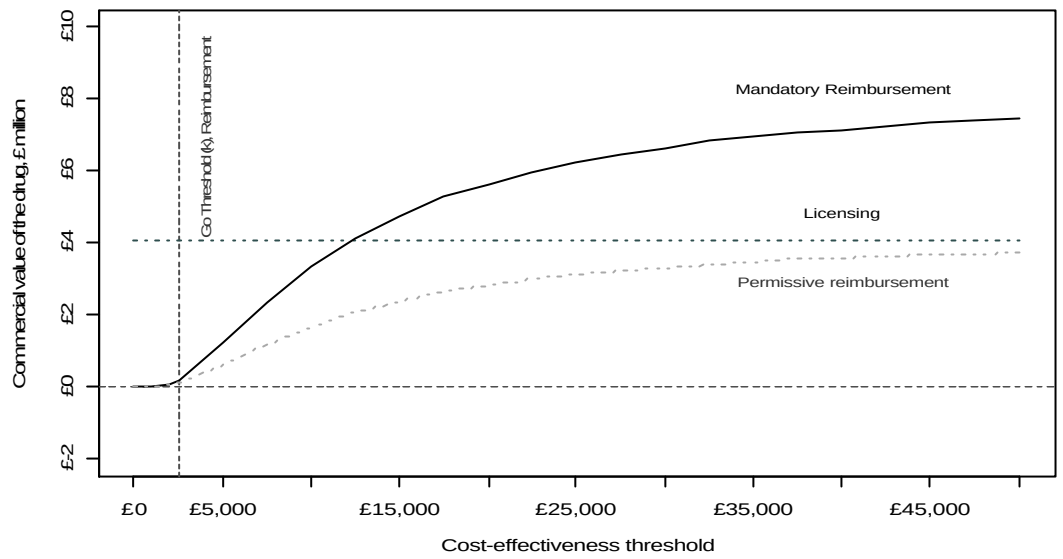
Under reimbursement, the cost-effectiveness threshold l directly determines $n_{r|l}(q)$; in addition, $R^- = 0$ always as $d_{r|l} | (lQ(q) < p) = 0$. The value of the drug is R^+, i.e.

$$u_{s,r} = \int_{lQ(q)>P} (lQ(q) - P) \left| (d_r = 1 \cap d_{r|l} = 1) \right. p(q)\, d(q) \tag{13}$$

As $u_{s,r}$ is always non-negative, a threshold k_r exists if $d_{r|l}(q) = 0$ always, hence $k_r \leq k_l$. Therefore, the term R^- is the difference between the value of the drug under licensing and under reimbursement, from which the value of the drug with any type of reimbursement is higher than under licensing, reflecting the value of averting realised negative net benefit. From $R^- = 0$ forgone opportunities associated with 'go' decisions under licensing are eliminated by the reimbursement rule.

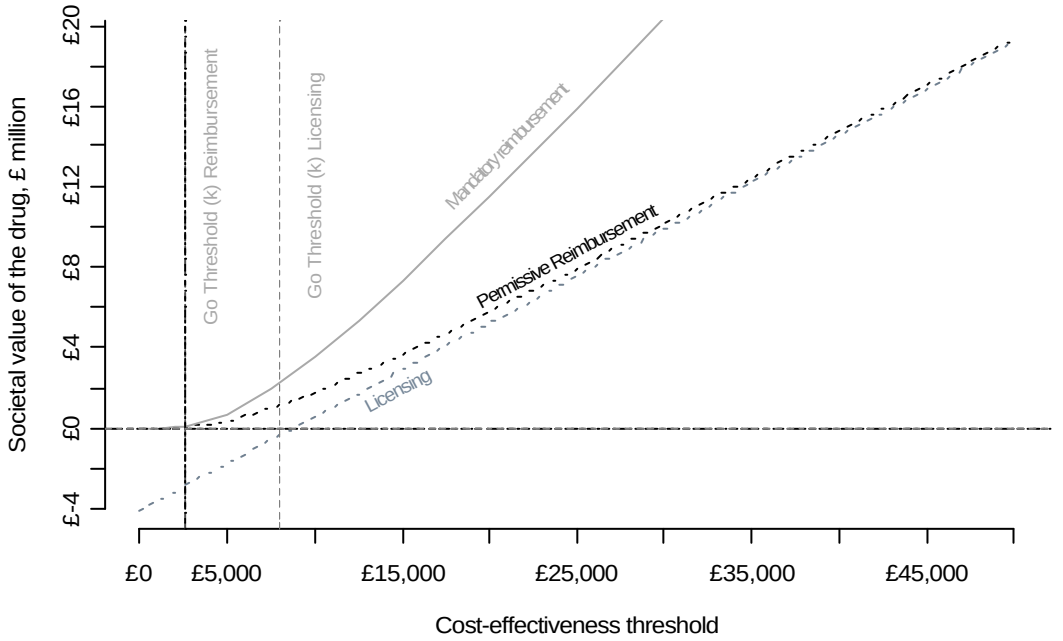
The value of the drug conditional on regulation and stop and go threshold for the societal decision maker are illustrated in Figure 2.

Figure 1 Commercial value of the drug under licensing, permissive and mandatory reimbursement



Expected total commercial value of the drug under licensing with price-sensitive coverage (dark grey dotted line); Reimbursement with price-sensitive coverage (light grey dotted line); Mandatory reimbursement with total coverage (black line); Commercial 'go' threshold k (vertical dashed line, at l=£2,000). All values calculated for 10,000 Montecarlo iterations; price= £550, total population N=30,000, demand d=0.5, prior distribution for effectiveness q obtained from prior relative risk of success with new drug (i.e. from a Phase II trial, RR=1.08, p=0.9094) with $q = f(q_{tr}, q_{pl}), q_{tr} \propto Beta(22,21), q_{pl} \propto Beta(19,21)$.

Figure 2 Societal value of the drug under licensing, permissive and mandatory reimbursement



Expected total societal value of the drug under licensing with price-sensitive coverage (dark grey dotted line); Reimbursement with price-sensitive coverage (black dotted line); Mandatory reimbursement with total coverage (grey line); Societal reimbursement 'go' threshold k (vertical black dashed line, at l=£2,000) is the same as the commercial; Societal licensing 'go' threshold k (vertical grey dashed line, at l=8,000). All values calculated for Montecarlo iterations, price, total population, demand and prior distribution for effectiveness as in Figure 1; $q = f(q_{tr}, q_{pl}, Q_{tr})$ *with prior relative risk of success as before and prior distribution for quality of life* $Q_{tr} \propto Gamma(2,4)$.

With licensing, stop decisions are taken at levels of cost-effectiveness conventionally considered 'good value for money'. Whether reimbursement is mandatory or permissive has no impact on the minimum cost-effectiveness threshold at which go decisions are supported, which depends on the probability of net benefit being positive only.

Mandatory reimbursement values a drug more reflecting its wider diffusion in the population. The value of the drug under mandatory reimbursement can also be interpreted as the maximum total willingness to pay for development reflecting exclusive access to the market.

APPLICATIONS

1. Does a licensing regime incentivise the societally optimal provision of information?

Using the framework above, we explore whether the licensing process provides adequate incentives to provide societally efficient information.

First, we assume that the demand of the drug is known. It is also necessary to consider the cost of drugs development, made up of (linear and additive) experimentation costs only. If we assume that the regulatory process provides no restrictions to the amount of information required beyond statistical significance, for example setting a clinically relevant effect size or power of experimentation, then a 'go' decision requires that commercial revenue is equal or higher than investment costs.

Under licensing, the value of the drug net of investment costs given known revenue PNd is $u_{c,l} = n_l(q) * PNd - I$ (Section 2.2.2), positive if $PNd > \frac{I}{n_l(q)}$ as $n_l(q) \neq 0$ always.

Therefore, for a regulatory rule t associated with a probability of acceptance $n_l(q)$ and no other restriction, a rational private agent can set a $I(n)$ and a postulated effect size upon which the hypothesis test t relies such that n is maximised with respect to $I(n)$ and a 'go' decision is always taken. This condition holds under uncertainty in the parameter q as $n_l(q)$ is the only source of commercial uncertainty. Increased uncertainty in clinical outcomes will be reflected in adjustments of the effect size chosen and in the amount invested $I(n)$.

This aspect of licensing explains behaviours such as prioritising new drugs for large markets despite small marginal improvements in effectiveness compared to the old, and its reverse, i.e. failure to develop drugs targeting small markets as their development may become economically unsustainable.

Proposed reforms to ensure more information around safety have included further restrictions to the hypothesis testing rule, i.e. extreme p-values[15] to reduce the type I error in the regulatory process, resulting in a reduction in $n_l(q)$.

In practice, we show above in a very stylised manner that the commercial economic return does not only depend on fixing a particular p-value only but also on the

postulated effect size tested in a trial. There are currently no regulatory restrictions around how the clinically meaningful effect size should be set, apart from calls to reasonability. On the contrary, the introduction of extreme p-values will decrease, but for reasons implicit in the nature of these errors, not eliminate type I errors at the cost of increasing the associated type II errors, i.e. the probability of rejecting alternative effective treatments. It has been advocated that prioritisation should be guided by a judgement based on societal benefit and taking the balance of benefits and risks into account, as restrictive release of new drugs may decrease adverse events in a few cases at the cost of preventing a much larger number of individuals who are able to benefit to do so.[16]

Another proposal would involve various forms of pre-licensing, for example conditional licensing[7] or withdrawal of market exclusivity agreements if information fails to be provided.[5] It is unclear how the latter proposal would reduce the risks that harmful drugs reach the market, as drugs with predictably few adverse events would be approved based on evidence, whilst drug with likely adverse events would be provided with a window of opportunity to access the market without licensing experimentation, with likely societal losses. Either proposals require a method to formally select the type of information required in support of the definitive licensing taking the balance of benefits and risks into account to guide research prioritisation.

2. The value of reimbursement regulation

This section illustrates some preliminary results around the value of efficient regulation in drugs development. This section develops the argument as follows: first, the societal and commercial value of regulation is described; then the societal value of reimbursement is calculated from the difference between the societal and commercial value of reimbursement minus the societal and commercial value of licensing. Unlike the case of optimal decision-making, the value of reimbursement regulation depends on coverage; therefore a distinction will be done between the values of permissive or mandatory reimbursement.

2.1. Societal net benefit with reimbursement

The societal value of reimbursement is equal to the difference between the societal value of the drug under reimbursement and under licensing,

$$\begin{aligned} R_s &= u_{s,r}\left|a_r - u_{s,l}\right|a_l \\ &= \max\left(0, u_{s,r}\right) - \max\left(0, u_{s,l}\right) \end{aligned} \qquad (14)$$

When coverage of the new drug is equal with reimbursement and with licensing, the value of reimbursement depends on the societal decision maker's willingness to pay for health gain and on the optimal development decision.

If the DM is willing to pay less than k_r, then both $u_{s,r}$ and $u_{s,l}$ are null and so is the value of reimbursement R_s.

For values of willingness to pay between k_r and k_l, the value of reimbursement $R_s = u_{s,r}$ is equivalent to the value of the drug under reimbursement, as a stop decision is taken under licensing.
For values of the willingness to pay above k_l, the value of reimbursement is equal to the value of opportunity losses under the licensing regime, i.e. the value of net benefit when the new drug would be licensed but not reimbursed. From (12) and noting that $u_s|d_l = 1$ can be rewritten as $u_s|\left(d_l = 1 \cap d_{r|l} = 1\right) \cup \left(d_l = 1 \cap d_{r|l} = 0\right)$ it is easy to see that the difference $R_s = u_{s,r} - u_{s,l}$ is equivalent to $-n_l(q) * \left(1 - n_{r|l}(q)\right) R^-$. This amount is always positive as $R^- < 0$ and $n_{r|l}(q) < 1$ always.

With mandatory reimbursement, the value of reimbursement remains null below k_r and equivalent to the value of the drug under reimbursement (inflated by the demand factor) in the range k_r and k_l. However, for values above k_l,

$$R_s = n_l(q) * \left((1-d) n_{r|l}(q) R^+ - d\left(1 - n_{r|l}(q)\right) R^-\right) \quad (15)$$

Mandatory reimbursement gathers value from both ensuring larger coverage and from reducing the risk of opportunity losses from the new drug.

2.2. Commercial benefit with reimbursement

Form the commercial value of regulation under licensing and under reimbursement, the value of reimbursement to the commercial agent is

$$\begin{aligned} R_c &= u_{c,r}|a_r - u_{c,l}|a_l \\ &= \max\left(0, n_l(q) * n_{r|l}(q) * PNd\right) - n_l(q) * PNd \end{aligned} \quad (16)$$

Unlike for society, the commercial value of reimbursement depends only on the reimbursement 'go' threshold k_r and coverage decisions only, as the commercial agent will always develop under licensing.
Below k_r, the commercial agent reports opportunity losses from reimbursement equal to the value of the drug under licensing, $R_c = -n_l(q) * PNd$
Above k_r, the value of reimbursement is

$$R_c = n_l(q) * \left(n_{r|l}(q) - 1\right) * PNd \quad (17)$$

and as $n_{r|l}(q) < 1$ always, the value of permissive reimbursement to the commercial agent is always negative.

In the case of mandatory reimbursement, the value to the commercial agent

$$\begin{aligned} R_c &= u_{c,m}|a_r - u_{c,l}|a_l = \\ &= n_l(q) * n_{r|l}(q) * PN - n_l(q) * PNd \end{aligned} \quad (18)$$

is a function of coverage and is positive for values of the probability of reimbursement given licensing such that $n_{r|l}(q) > d$. Therefore the commercial value of reimbursement depends on the balance between the market quota and the probability of reimbursement given that a drug is licensed.

2.3. Total benefit from a reimbursement regime

The net value of the reimbursement regime $R_w = R_s + R_c$ is an indicator of whether the reimbursement regime favours drug development. To analyse the value of a reimbursement regime we need to distinguish three cases.

Below k_r, $R_w = -n_l(q) * PNd$ as $R_s = 0$. Therefore when the reimbursement regime values health gain too little, regulating reimbursement is likely to prevent drugs from being developed, compared to licensing.

Between k_r and k_l, from (13) and (18)

$$R_w = n_l(q) * \left(n_{r|l}(q) - 1\right) * PNd + n_l(q) * n_{r|l}(q) * R^+ \qquad (19)$$

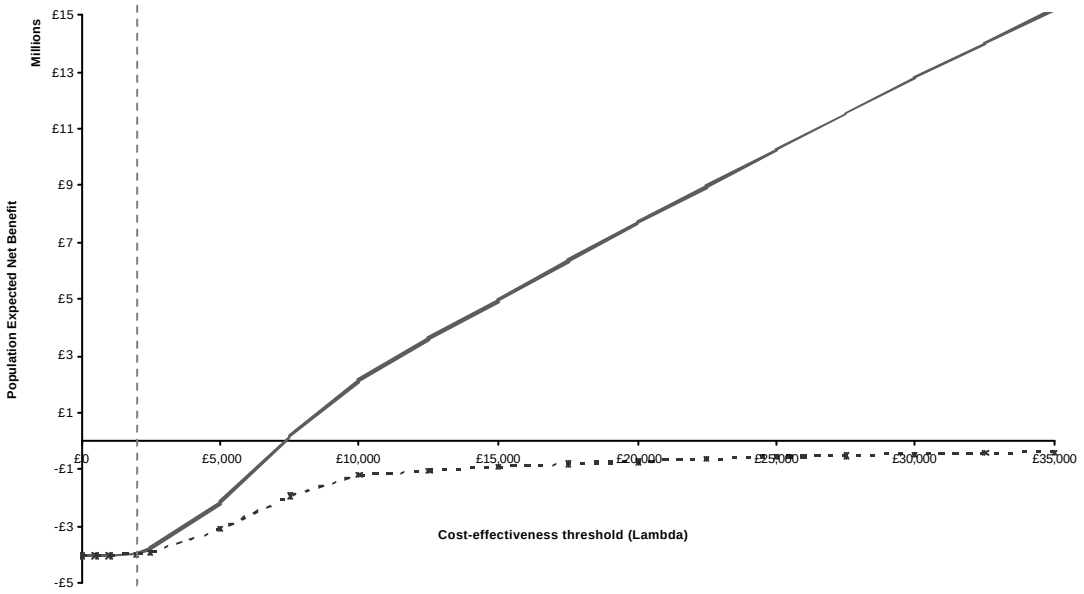
and above k_l, from (15) and (18)

$$R_w = n_l(q) * \left(n_{r|l}(q) - 1\right) * PNd - n_l(q) * \left(1 - n_{r|l}(q)\right) R^- \qquad (20)$$

The sign of this difference depends on the comparison of the absolute value of PNd with respectively, R^+ and R^-. In general, the value of reimbursement depends on the elasticity of coverage with respect to price, in a permissive reimbursement regime, and the price of the drug. In the subsequent pricing section, we show that if the commercial agent can capture the value of societal benefit in the price of the drug, the value of reimbursement is positive.

The graphical representation of the value of a reimbursement regime is illustrated in Figure 3.

Figure 3 Value of reimbursement regime, permissive and mandatory reimbursement



Expected value of reimbursement with price-sensitive coverage (dark dotted line); Mandatory reimbursement with total coverage (black line); Societal reimbursement 'go' threshold k (vertical grey dashed line, at I=£2,000) Values calculated as in previous Figures 1 and 2

3. Pricing drugs during development

In previous Sections we ignored the role of demand on commercial and societal rewards and we assumed that the profit-maximiser commercial agent would set a price p_l where demand is unit elastic $\left(e = \frac{-dQ/q}{dP/p}\right)$ with respect to price, i.e. at prices higher or lower than p_l the total revenue for the drug is decreased.

In practice the drug price p_l is set after the drug is licensed, whilst reimbursement is evaluated once the drug is licensed and priced. Let us now assume that a drug licensed at this price is submitted for reimbursement. At the licensing price p_l a licensed drug can be reimbursed or not, therefore at such price, the value of the drug under reimbursement is lower than that under licensing. This is easily verified rewriting the value under licensing as

$$u_{c,l} = \int_{lQ(q)>p_l} p_l N d(d_l \left| d_{r|l}=1\right) d(q) + \int_{lQ(q)\le p_l} p_l N d(d_l \left| d_{r|l}=0\right) d(q) \qquad (21)$$

from (11) and noting that the second term in (21) becomes null under reimbursement, with forgone revenue equal to the latter term (in absolute terms).

3.1. Commercial value-based optimal price

It the commercial decision maker had perfect information around the distribution of q, then for each value of ? at which $d_l = 1 \cup lQ(q) \le p_l$, reimbursement could be achieved with a reduction in price such that $p \to lQ(q)^-$.[3] Therefore for any potential realisation of uncertainty, a demand-constrained commercial maximiser will set a price such that $p^* = \max(p_l, lQ)$, with total expected NPV (Figure 4) equal to

$$\begin{aligned} u_{c,r} &= \int_{lQ(q)>p_l} p_l N d(d_l \left| d_{r|l}=1\right) p(q) d(q) + \int_{lQ(q)\le p_l} lQ^* N d(d_l \left| d_{r|l}=1\right) p(q) d(q) = \\ &= \int_{-\infty}^{+\infty} \max\left(p_l, p^*\right) N d d_l \, p(q) d(q) \end{aligned} \qquad (22)$$

as if $lQ(q) > P$, $n_r(q) = n_l(q)$ and $d_{r|l}(q) = 1$ always. As a result, the stop region under reimbursement is removed. The pricing decision therefore conditions the investment decision, as the commercial decision maker can always set a price that will make the 'go' decision the optimal decision for any value of q.

If the demand constraint is not binding, as in a mandatory reimbursement regime, then the pricing decision $p^* = \max(p_l, lQ)$ is suboptimal and contradicts the fully informed agent condition. With perfect information around each value of ? for which

[3] Strictly speaking at a price $p = lQ(q)$ the drug is not reimbursed as NB=0. However to simplify notation in the rest of the Section the superscript is dropped and the equal sign is used throughout. The results around pricing should then be interpreted as the approximate upper bound for pricing decisions.

$d_l = 1 \cup lQ(q) > p_l$, an increase in price to $p^* = lQ$ would be supported by the reimbursement condition, with maximum commercial expected NPV equal to $u_{c,t} = N \int_{-\infty}^{+\infty} lQ d_l(q) d(q) = N\, lQ u_l(q)$ (Figure 4). The commercial value of the drug is equal to the societal value of the health benefit if the drug is licensed, i.e. the societal value of the drug with licensing, inflated by the licensing price.

3.2. Societal benefit at commercial value-based optimal price

The societal net benefit at the commercial optimal price is null, as $p^* = lQ(q)^-$ is only another way to write $lQ(q) - p^* = 0$. Therefore the societal expected net benefit conditional on a demand constrained reimbursement regime is unchanged with and without value-base pricing. Rewriting the societal value of the drug under demand constrained reimbursement as

$$\begin{aligned} u_{s,r} &= \int_{lQ(q)>P} d(lQ(q) - P) d_l d_{r|l}(q) d(q) = \\ &= \int_{lQ(q)>p_l} d(lQ(q) - p_l) * (d_l | d_{r|l} = 1) d(q) + \int_{lQ(q)\le p_l} d\left(lQ(q) - p^*\right) * (d_l | d_{r|l} = 0) d(q) \end{aligned} \quad (23)$$

with the last term is always null at $p^* = lQ(q)$. This shows that, regardless of the empirical form taken by uncertainty, society is indifferent to which pricing regime is adopted under permissive reimbursement, as the pricing decision will not change the value of the drug to society nor the optimal stop or go decision.

Under value-based pricing and mandatory reimbursement, then it is immediate from $lQ(q) - p^* = 0$ that $u_{s,r} = 0$ independently from the probability of licensing and despite certain reimbursement if the drug is licensed. Society becomes indifferent to having a drug or not under a mandatory reimbursement regime where the pricing mechanism allows total commercial capture of the total consumer surplus.

4. The value of combined reimbursement-pricing regime

We distinguish two combined regimes of permissive or mandatory reimbursement and value-based pricing (VBP).

With permissive reimbursement and value based price (Figure 5), the difference between the commercial value of the drug under licensing and under reimbursement is driven by the decrease in revenue in any iteration where reimbursement would be denied at the licensing price but is granted at VBP. As at VBP the total revenue is lower despite a larger demand, the commercial value of reimbursement is equal to

$$R_c = \int_{lQ(q)\le p_l} d^* p^* - d p_l (d_l | d_{r|l} = 0)\, p(q) d(q) < 0 \quad (24)$$

The societal value of reimbursement on the contrary does not change in relation to the pricing regime (as is (23) above). Therefore, considering that $p^* = lQ$ and that the demand for the drug at p^*, d^*, can be rewritten as $d^* = d + \Delta d$, the total benefit from mandatory reimbursement and value-based pricing is equal to

$$
\begin{aligned}
R_w &= \int_{lQ(q)>p_l} d(lQ(q)-p_l)\left(d_l \middle| d_{r|l}=1\right)p(q)d(q) + \int_{lQ(q)\le p_l}\left(d^* p^* - dp_l\right)(d_l \middle| d_{r|l}=0)p(q)d(q) \\
&= \int_{-\infty}^{+\infty} d(lQ-p_l)d_l\, p(q)d(q) + \int_{lQ(q)\le p_l} \Delta d p^* p(q)d(q) \\
&= u_{s,l} + \int_{lQ(q)\le p_l} p_l\left(1-\frac{1}{|e|}\right)p(q)d(q)
\end{aligned}
\tag{25}
$$

Therefore, the value of reimbursement is equal to the societal value of the drug under licensing plus a factor equal to the value of the health gain proportional to the associated increase in the diffusion of the drug in the population.

Above the licensing threshold, it is equal to the value of opportunity losses a proportion of which, equal to $d^*(p^* - p_l)$ is captured by the commercial agent.

Overall, the increased value of the treatment is entirely captured by the commercial agent, therefore the increased value of reimbursement arises from a net transfer from society to the commercial agent equal to the value of increased diffusion of the drug, at lower prices.

Under a mandatory regime (Figure 6) the societal value of reimbursement and value based price is equal to

$$
\begin{aligned}
R_s &= u_{s,r}\left|a_r - u_{s,l}\right|a_l \\
&= 0 - \max\left(0, u_{s,l}\right) = \min(0, -u_{s,l})
\end{aligned}
\tag{26}
$$

Therefore the societal value of VBP is negative above the 'go' licensing threshold.

The commercial value of reimbursement and VBP is equal to

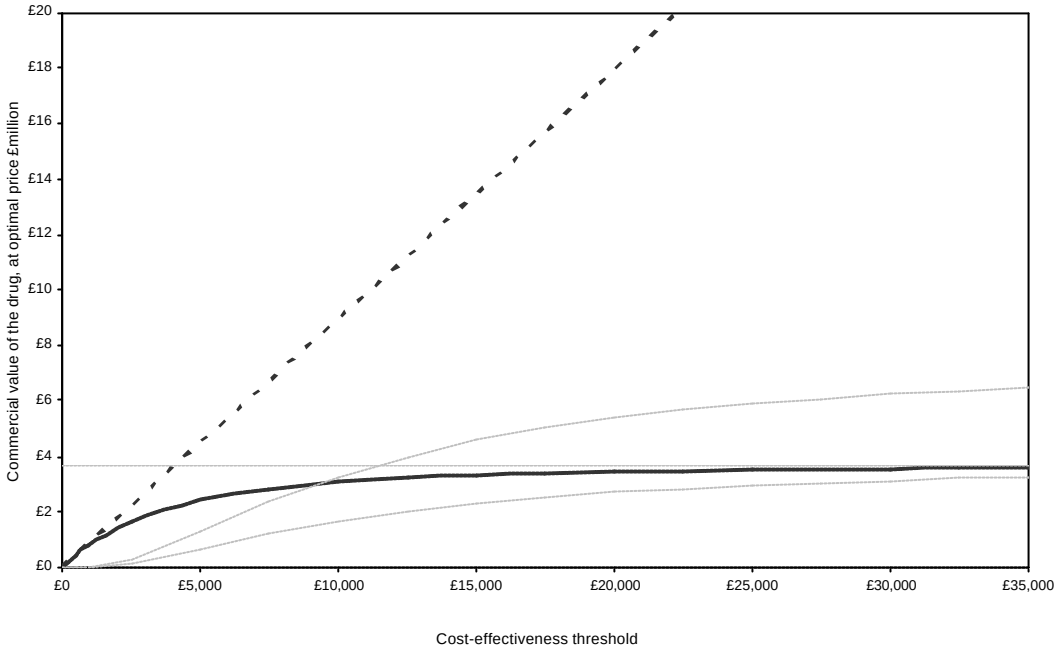
$$
\begin{aligned}
u_l(q)lE(Q) - u_l(q)dp_l &= \int_{-\infty}^{+\infty} d(lQ-p_l)d_l\, p(q)d(q) + \int_{-\infty}^{+\infty}(1-d)\,lQ d_l\, p(q)d(q) \\
&= u_{s,l} + (1-d)\,lE(Q)
\end{aligned}
\tag{27}
$$

which shows that the societal value of reimbursement i.e. the benefit accrued by extending the market to cover the whole population is entirely captured by the commercial agent.

Therefore the overall value of VBP below the licensing threshold is made up by the societal value of the drug under licensing and a factor equal to the price of the drug constrained or unconstrained by demand, i.e. the net benefit or the licensing price, whichever is greater.

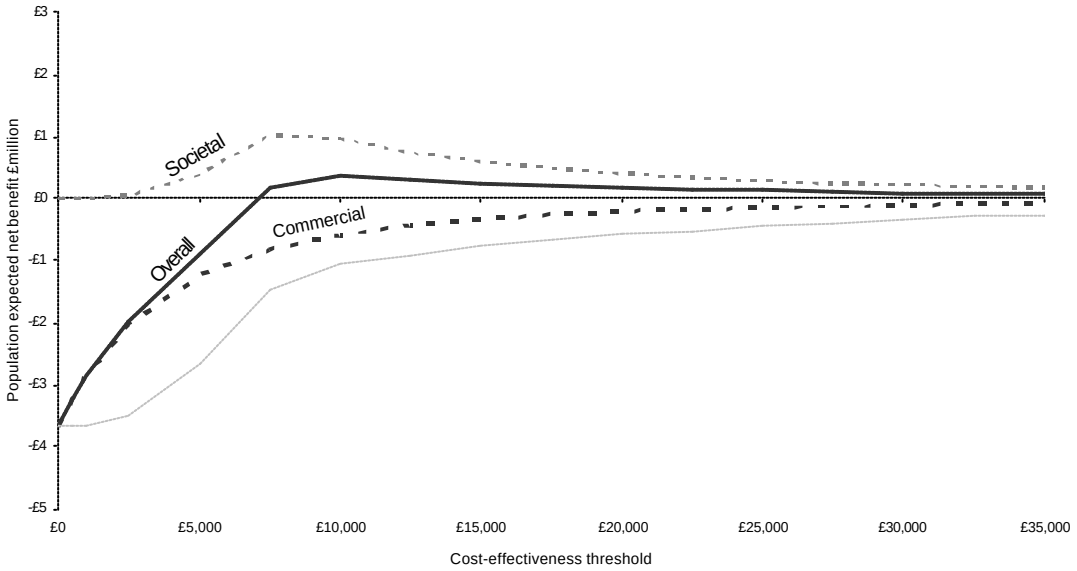
Above the licensing threshold, the value of reimbursement is a function of the societal value of the net benefit forgone under licensing, partially or wholly captured in the price of the drug, and depending on market constraints. This shows that VBP and the reimbursement rule are substitutes, and that with VBP the value of health gain is captured by the commercial agent.

Figure 4 Commercial value of the drug with value-based price (VBP) and permissive or mandatory reimbursement



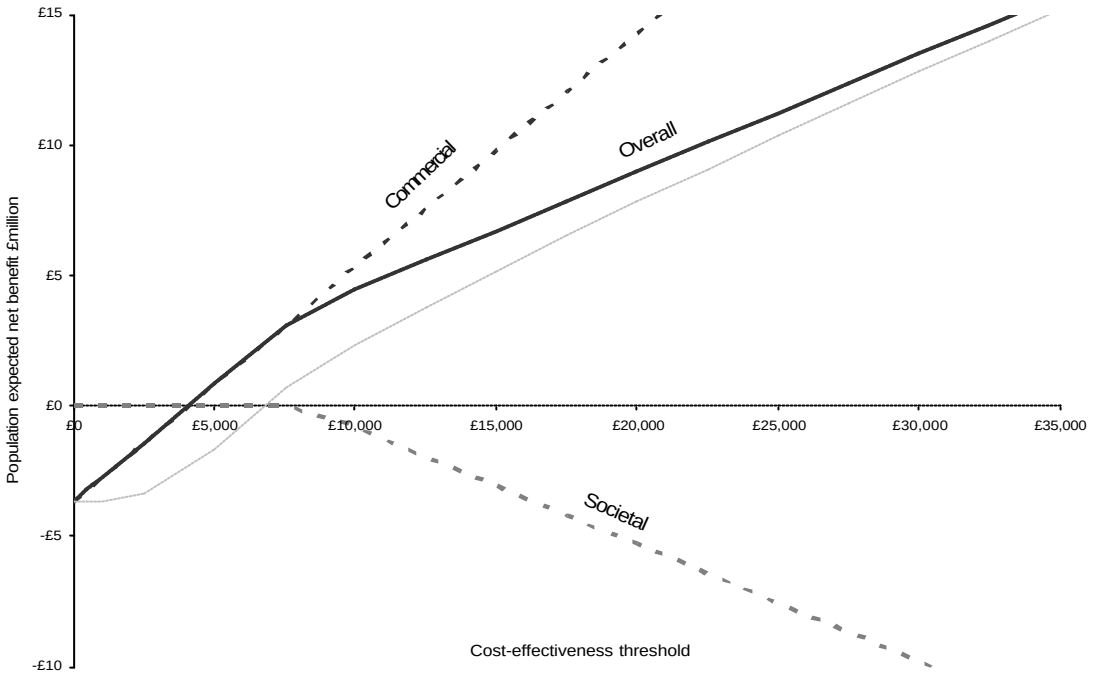
Expected commercial value of the drug with VBP and permissive reimbursement (black line); VBP and mandatory reimbursement (black dotted line); Expected commercial value of the drug with licensing price (grey lines in background, as in Figure1: licensing with demand constraints, reimbursement with or without demand constraints); Values calculated as in previous Figures 1 and 2

Figure 5 Value of permissive reimbursement regime combined with value-based pricing (VBP)



Expected value of permissive reimbursement with VBP (black line, overall); societal value of reimbursement with VBP (grey dotted line, societal); commercial value of reimbursement with VBP (black dotted line, commercial); Expected value of permissive reimbursement at licensing price (grey line in background, as in Figure 3); Values calculated as in previous Figures 1 2 and 3

Figure 6 Value of mandatory reimbursement regime combined with value-based pricing (VBP)



Expected value of mandatory reimbursement with VBP (black line, overall); societal value of reimbursement with VBP (grey dotted line, societal); net commercial value of reimbursement with VBP (black dotted line, commercial); Expected value of mandatory reimbursement at licensing price (grey line in background, as in Figure 3); Values calculated as in previous Figures 1, 2, 4 and 5

CONCLUDING REMARKS

We have examined the incentives of commercial and societal agents to develop a new drug when access to market is regulated by a simple licensing regime or by a combined licensing and reimbursement regime, both demand-constrained and with mandatory coverage.

The commercial incentives implicit in a licensing regime are not sufficient to reflect societal prioritisation mechanisms, as incentives do not reflect the uncertain benefit brought about by a drug. As a result, the licensing regime may encourage inefficient allocation to developing new drugs that may not be successful, and in addition cause misallocation of resources to research with no practical reduction in uncertainty in the go/no-go decision.

This argument has proven a popular argument for a call in reduction of regulation in the pharmaceutical sector. For example, Peltzman et al[9] stated that regulation of the pharmaceutical market imposes high costs with little societal gain. The authors assessed the value of regulating developed drugs based on changes in the demand for new drugs after the introduction of licensing regulation in the US, and found that as demand did not change before and after, the gains from regulation were small compared to the societal opportunity losses from undeveloped drugs. However their analysis only shows that the number of drugs submitted for approval decreased, suggesting that regulation deters the submission of drugs with low societal value that

would otherwise be developed, rather than necessarily increase the production of innovative drugs for the whole sector.

Our analysis starts from a different perspective and involves the assessment of the value of a new drug before development, including uncertainty in the regulatory process in the value of the drug, therefore the incentives of the commercial agent to develop and of the societal to accept the new drug are based on the prediction whether a new drug is innovative or not compared with the status quo.

Compared to the licensing regime, reimbursement improves the societal but decreases the commercial incentives to develop a new drug. We also show that the net benefit associated with a demand-constrained reimbursement regime may not be compensated by the opportunity loss imposed to the commercial agent. However it would not be correct to conclude that reimbursement imposes societal losses.

First, commercial losses can be compensated with increased coverage associated with mandatory reimbursement, reflecting the societal benefit from increased consumption. Second, a combination of reimbursement and pricing compensates partially or entirely commercial opportunity losses. Therefore the reimbursement regime offers an option to society to accept drugs of higher benefit, and although there are commercial opportunity costs associated with this option, the commercial sector can still be compensated with improved access to market and or capture of consumer surplus. At the extreme case of the value-based pricing regime associated with reimbursement where the entire consumer surplus is transferred to the commercial agent, the producer's incentives to develop a new drug are maximised, although with no residual benefit accrued by society the latter is indifferent to obtaining such drug or not. As the consumer surplus is large, a compensation mechanism can be found that allows the consumer to retain some of the value created so that incentives remain aligned for the commercial and society decision-maker alike.

Finally, our model did not consider the role of the information conveyed from regulatory experimentation necessary to develop the drug. From the perspective of the bureaucrat, experimentation counts only towards the deterministic aim of succeeding regulation hurdles and reduce regulatory errors.[17] However to fulfil the rationality and full information criterion, a model of development choices must account for the informative content of experimentation generated during the development process. Accruing information is an irreversible act as the agent cannot revert to a state of ignorance once information is available.[18] Further, investments in drug development are sunk and mainly made up by experimentation costs therefore information and development costs are interdependent and both depend on commercial development choices. Therefore a predictive model of optimal development choices requires the incorporation of imperfect information accrued during development experimentation,[19] that will be pursued in a following paper.

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