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New compound real option pricing methodology with Lévy processes for valuation and risk management of multistage pharmaceutical R&D

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The objectives

We present a new methodology for valuation of compound barrier real call options by R&D stages with Lévy underlying processes

This novel proposal is needed to tackle urgent R&D management challenges with:

(i) cost-efficacy thresholds for reimbursement of medicine introduced by several countries, including the UK,

(ii) designing a foundation for the model-informed drug development by incorporation of pharmacology and commercial thresholds,

(iii) fair R&D valuation to enable pharmaceutical companies to issue and trade call options at each R&D stage to attract additional needed investment.

The roadmap

- ✓ A summary of methods, results, and conclusions
- ✓ The motivation for the proposed method
- ✓ A brief overview of the real option approach to multistage R&D projects
- ✓ Our contribution: new evaluation method of the barrier options with new underlying - Lévy processes
- ✓ An illustration of the proposed method to price a Vitosha's pharmaceutical R&D project with a focus on drug efficacy threshold
- ✓ Conclusion: we propose a new financial instrument to democratise and disrupt both financing and management of R&D in the industry

A summary of methods, results, and conclusions

METHODS:
In the proposed integrated quality-by-design real option model, we put new drug efficacy at the center of the entire R&D process. We model the drug efficacy dynamics with new methodology with Lévy underlying processes and provide a road map of expected losses and success rates for each R&D stage. The model allows to control the ratio of the compound R&D option value to the expected losses with pre-set efficacy thresholds for a new product. The approach incorporates multiple technological and commercial shocks in line with the value-for-money R&D framework.

RESULTS:
We have derived an iterative formula for estimation of volume and price of the proposed real call options for pharmaceutical R&D projects for each stage conditional on obtained R&D results in real time. We numerically demonstrate viability of the proposed compound call options for the typical industry R&D project.

CONCLUSION:
The stage R&D real call options can provide an attractive solution for the deficiency of R&D financing, as well as to develop new medicine in line with set national efficacy thresholds. Using the proposed model, drug developers can issue the compound call options to cover expenses at each R&D stage, if a drug candidate demonstrates safety and efficacy. This can alleviate the “value of death” problem in drug R&D financing.

Motivation

- ✓ **A number of diseases and drug classes have acute deficiency of new medicine with little R&D financing due to small markets, high costs and risks of drug development**

Well known examples are vaccine development, orphan, and neglected diseases for many dozens of conditions affecting lives of billions of people, for whom the standard business model often fails to provide quality medicine. Lo (2021) calls to the profession to design new models

- ✓ **New pharmaceutical R&D business/economics models are needed due to the decline of the R&D productivity in the industry, which is of high global concern**

The decline is alarming as Scannell et al., (2012: 191) conclude that "…*the number of new drugs approved per billion US dollars spent on R&D has halved roughly every 9 years since 1950, falling around 80-fold in inflation-adjusted terms*". Munos' (2009: 959,967) analysis of the major pharmaceutical companies since 1950 comes to a similar conclusion: "The R&D model … is showing signs of fatigue: costs are skyrocketing, breakthrough innovation is ebbing…". A comprehensive study of drug candidates shows that the decline is likely to be associated with a shift towards more risky projects with less known medical mechanisms (Pammolli et al., 2011).

The *Prescrire International Outlook* has calculated the share of new drugs in France that is either "*nothing new*" or "*not acceptable*" over **60%** in the last two decades!

Motivation (continued)

- ✓ Developing better R&D management tools to address growing medical of rapidly ageing population and new pandemics. The European Federation of Pharmaceutical Industries and Associations calls for **new model-informed drug development** "aimed at improving the quality, efficiency and cost effectiveness of decision making" (Marshall et al., 2016: 94).
- ✓ Particular challenges are incorporation of both pharmacological and financial product performance variability (Huchzermeier and Loch, 2001; Bonate, 2011: 543-544) with asymmetric downward risks when safety, efficacy, and expected sales of drug candidates drop below critical thresholds
- ✓ The current NPV approach is typically misleading for long R&D projects, especially as the average industrial IRR is just around 1.2% (Deloitte, 2023)
- ✓ As some countries have set specific cost thresholds per QALY saved as the pre-requisite for public reimbursement of medicine, the NPV approach is not up to this challenge. For example, Britain sets this threshold at £30,000 per QALY, Ireland – at €20,000
- ✓ Ad-hoc real option models with unrealistic assumptions such as the geometric Brownian motion of the underlying R&D process and only cost dimensions limit their applications

The real option approach to multistage pharmaceutical R&D projects

- **To address contingencies of the R&D process in a product valuation**
- **Real option to expand** – a right but not an obligation to make an investment into the next stage of a new drug development
- **Compound option** – option on an option to invest into further R&D stage
- **Methods** – the financial theory of pricing financial options, but instead of the stock price movement, the real option approach models ***the underlying*** R&D project valuation random process

The existing real option models: major drawbacks

- The underlying process is ***an artificial random process*** V_t: the main focus on the financial dynamics of the estimated net present value (NPV) of a new drug net sales during the drug development stages
- V_t is modelled as a geometric Brownian motion, which is ***"too smooth"*** to account for the real sudden changes in the NPV and R&D events
- A typical R&D project manager ***does not re-estimate the NPV*** in real time

A compound real option approach with 6 stages of drug R&D

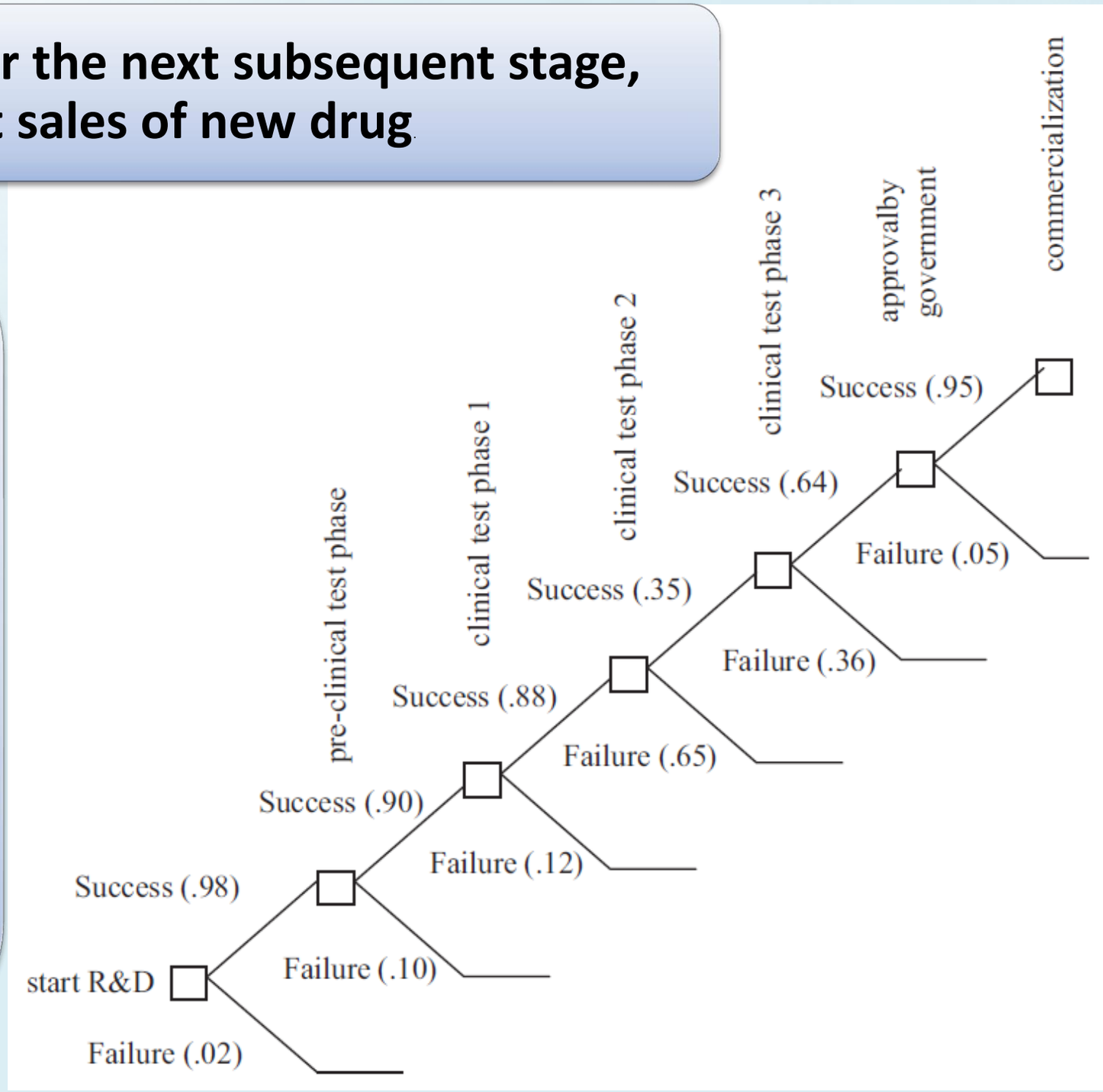
we use the example of drug R&D project provided by *Cassimon et al., (2011)* in *Research Policy* journal, but with new proposed methodology

At each stage, an option is written for the next subsequent stage, and the last stage is an option on net sales of new drug

New parameters in our model:

The R&D project stops if the drug candidate fails at the stage $i-1$ on:

i. safety such as excessive toxicity or side effects
ii. low relative efficacy in comparison with a benchmark
iii. commercial reasons, if the current project value is less than investment for the stage i



Our model uses new underlying - Lévy processes

- Lévy processes in real options theory have been virtually absent, but such processes better incorporate jumps in R&D process
- We incorporate the stochastic new drug efficacy process with jumps reflecting new project's R&D process information flow
- We allow for jumps in the quality of a new drug as measured by management set thresholds in new medicine (i) safety, (ii) efficacy, and (iii) expected sales against a benchmark
- We focus on a drug candidate's relative efficacy process

$X_t = \ln(E_t/B)$, where E_t is the current efficacy of a drug candidate, and B is the efficacy of a benchmark drug/treatment

- The efficacy X_t follows the Poisson process with rate λ and random jumps Y_i, which are i.i.d.: $X_t = \sum_{i=1}^{N_t} Y_i$
- Project fails either due to low relative efficacy or if its commercial value $V_i(t, x, V) < K_i$ - costs for an R&D stage i

The proposed new real option model

The net present value in the last stage 6 at time T_6: NPV_{T_6} is a product of

- ✓ **Efficacy indicator, which follows exponential compound Poisson model $\exp(X_t - x_0)$ with discrete jumps in efficacy from t $= 0$ till T_5),**

$X_t = \ln(E_t/B)$ **relative efficacy**

- ✓ **Value process (follows Black-Scholes model $e^{Z_{T_6}-T_5}$ from t $= T_5$ till T_6)**
- ✓ **Average NPV (V)**
- ✓ **Safety indicator (0 or 1): s_i - related safety probability at stage i**
- ✓ **Inflation minus capital discounting rate (e^{qT_6})**

Compound option prices $V_i(T_{i-1}, x, V)$ at stages $i = 1, \dots, 5$ and 6

$$V_i(T_{i-1}, x, V) = e^{-r(T_i - T_{i-1})}\mathrm{E}\left[\left(V_{i+1}\left(T_i, X_{T_i}, V\right) - K_i\right)_+ \cdot I_{X_{T_i} > h_i} \middle| X_{T_{i-1}} = x\right] s_i,$$

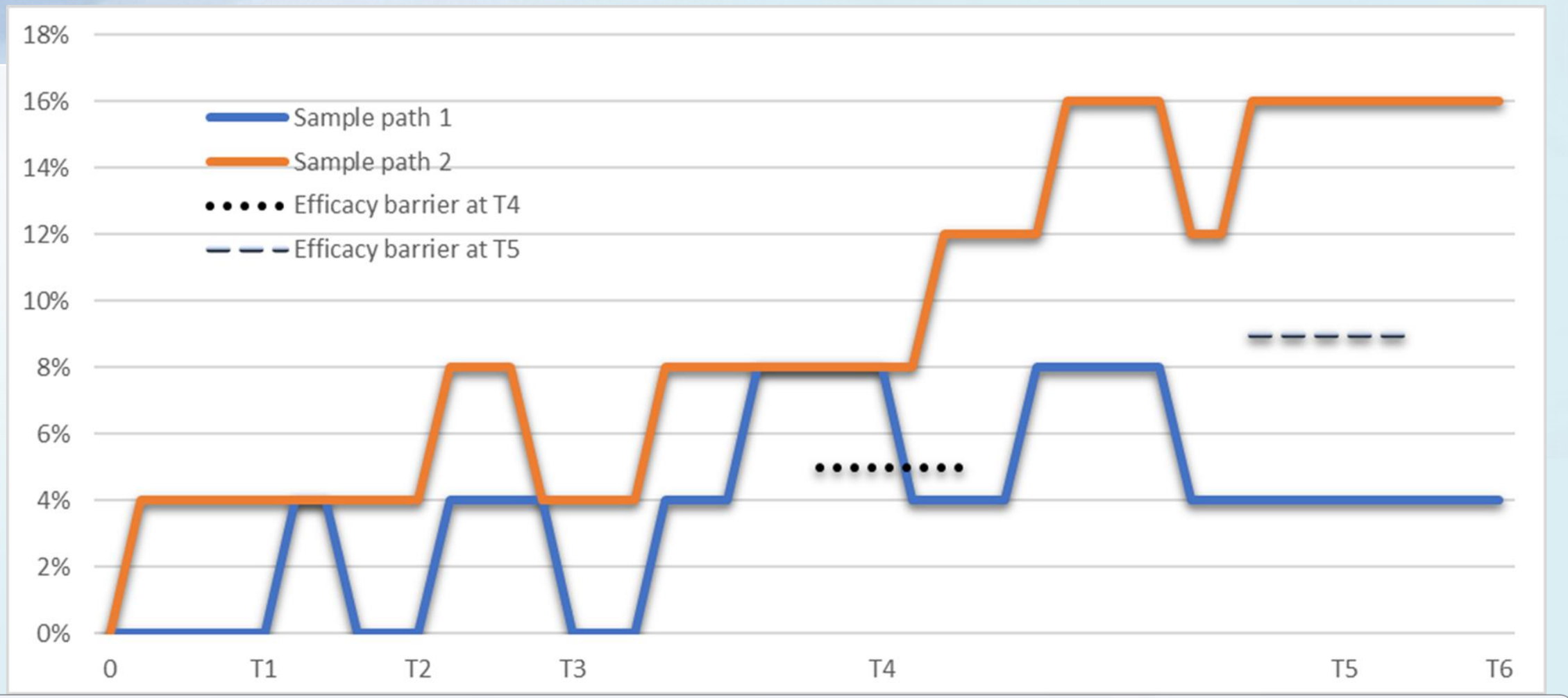
$$V_6(T_5, x, V) = \mathrm{e}^{-r(T_6 - T_5)}\mathrm{E}\left[\left(\mathrm{e}^{qT_6} V \mathrm{e}^{Z_{T_6}-T_5} \mathrm{e}^{x - x_0} - K_6\right)_+ \middle| Z_0 = 0\right] s_6 \cdot I_{x > x_0}$$

T_i is the maturity of the compound call option V_i at stage *i* = 1, …6

K_i is the exercise price (investment) at stage $i + 1$

h_i is the efficacy barrier at stage *i* = 1, …6, which can be set by a manager

Example. Sample paths of efficacy X_t with the efficacy barriers h_4 and h_5 in periods T_4 and T_5, respectively



Sample paths of efficacy X_t are comprehensive for the manager w.r.t. GBM

	T_4 (Clinic phase II of the R&D has been finished)	T_5 (Clinic phase III of the R&D has been finished)
Sample path 1	efficacy is over the barrier h_4	efficacy is under the barrier h_5
Decision	start Clinic III	stop the project
Sample path 2	efficacy is over h_4	efficacy is over h_5
Decision	start Clinic III	start Approval phase

Assumptions for the numerical estimations of the commercial pharmaceutical R&D project

We use the numerical example of Vitosha's pharmaceutical R&D project as described by Cassimon et al., (2011) and fit the parameters to our method

The instantaneous standard deviation of the project returns during the approval phase is assumed to be 0.976. The risk-free interest rate is 4.84%

We assume that the minimal relative efficiency $x_0 = 8\%$ required for the drug approval by authorities is equivalent to the efficacy barrier h_5 at stage 5

News about a drug candidate arrive annually: $\lambda = 1$ for simplicity

The annual inflation of drug prices: $q = 10\%$

Upward (downward) jumps in efficacy: plus or minus 4% with probability 60% up and with probability 40% down

The estimated parameters of Vitosha's pharmaceutical project with the proposed new methodology focused on drug efficacy with Lévy processes (in million US$)

R&D stage	Year start	Year finish	T_i	K_i	s_i	e_i	p_i	h_i	V
Decision to start (t = 0)	2003		0	10					
Stage 1: Discovery	2003	2004	1	10.3	98%	100%	98%		
Stage 2: Pre-clinical stage	2004	2005	2	13.2	90%	100%	90%		
Stage 3: Clinical phase I	2005	2006	3	37.3	88%	100%	88%		
Stage 4: Clinical phase II	2006	2008	5	160.6	86%	41%	35%	5%	
Stage 5: Clinical phase III	2008	2011	8	48.7	89%	72%	64%	8%	
Stage 6: Drug approval and launch	2011	2012	9	38.9	95%	100%	95%		
	2012								376.3

The estimated compound option prices by R&D stages for relative efficacy levels: Vitosha's project, million dollars

R&D stages	Relative efficacy										
	0%	4%	8%	12%	16%	20%	24%	28%	32%	36%	40%
Stage 1: Discovery	18.3										
Stage 2: Pre-clinical	15.2	53.1	103.8	156.5	202.6	238.2	263.2				
Stage 3: Phase I	9.6	54.5	119.0	186.8	244.9	288.7	319.8	340.0			
Stage 4: Phase II	0.00	53.5	138.8	229.4	304.7	359.0	396.8	423.5	439.7		
Stage 5: Phase III	0.00	0.00	167.3	323.4	438.0	507.4	551.6	586.5	617.4	640.9	643.8
Stage 6: Approval and launch	0.00	0.00	0.00	793.6	829.4	866.6	905.4	945.8	987.8	1031.6	1077.1

Project value – $18.3 million ($19.5 million without efficacy barriers)

New estimations of the unexplored aspects of R&D projects in real options – the expected losses – $39 million ($50.7 million without efficacy barriers)

Compare with the project value in Cassimon et al., (2011) – $22.61 million

Conclusion: New financial instrument to democratise and disrupt the industry

- We developed a modification of the call option idea with writing a call option on a share of expected new medicine to be sold, which makes call option cheaper and more accessible for smaller investors from developing countries.
- Let C_i be the price of compound call option for the $i+1$ R&D stage, and K_i be investment (costs) of R&D at stage $i = 1,2,3,4,5$
- If the project is profitable, the medicine developer issues call options for x_1 share of the net sales of new drugs, $0 < x_1 < 1$, to meet the expected costs of that R&D stage
- If the first R&D stage is successful, the call option C_1 also gives the right (not an obligation) to buy new call option C_2 for the next R&D stage with K_2 R&D costs
- If the project is perspective, the drug developer gets $x_1 K_2$ from the call option C_1, while external investors obtain call value $x_1 \mathrm{C}_2$
- For the second R&D stage developers issue calls in amount of $(1 - x_1)K_2$ for the 3rd R&D stage with x_2 share, $0 < x_1 + x_2 < 1$. Again, x_2 is defined to meet R&D costs for the stage, and continue iteratively issue call options for each R&D stage
- The control and transparency of this new call option market can be secured with a blockchain platform to resolve multiple financing and quality assurance mechanisms