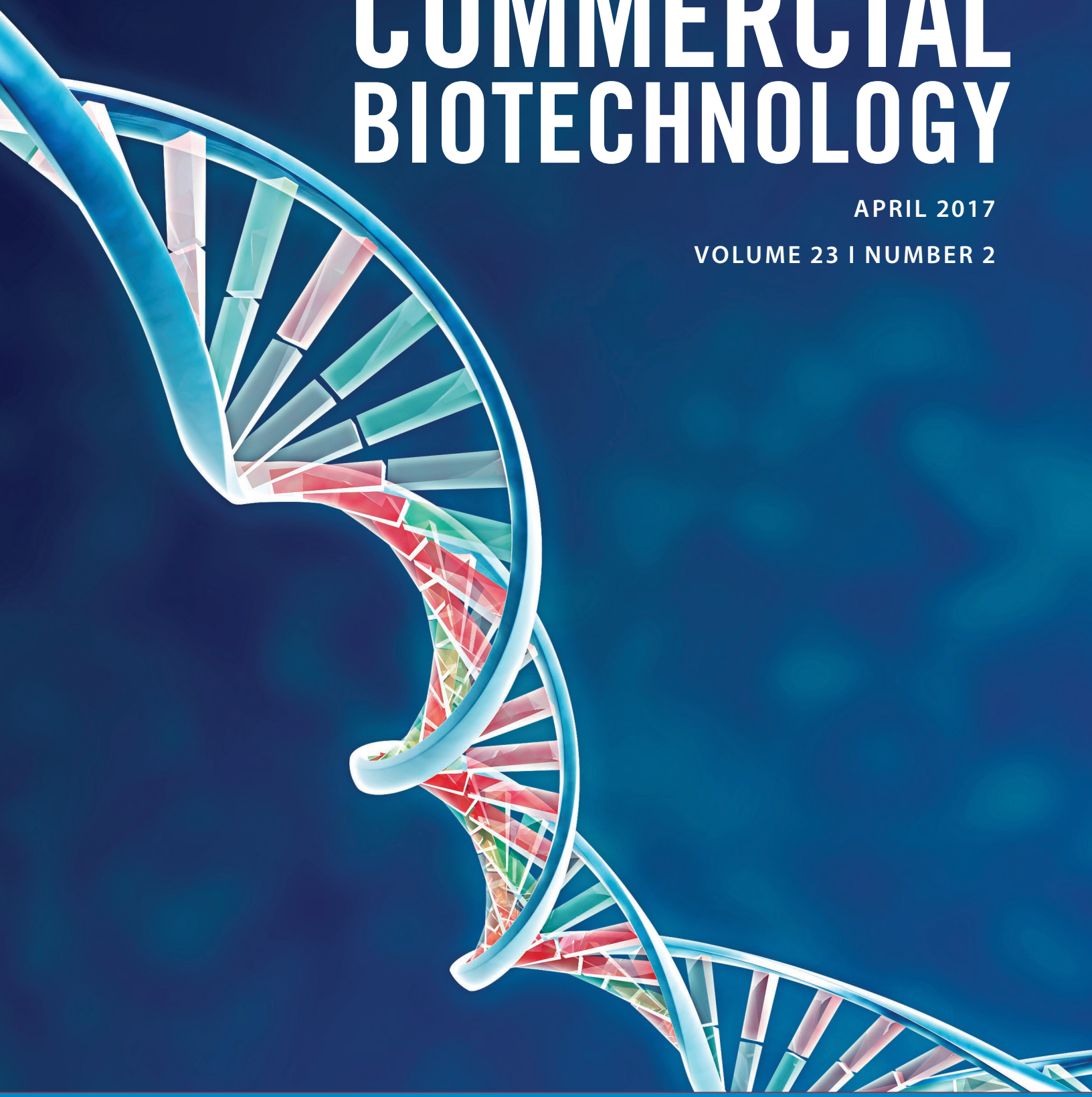
Journal of COMMERCIAL BIOTECHNOLOGY

APRIL 2017

VOLUME 23 I NUMBER 2



ISSN: 1462-8732 / eISSN 1478-565X

WWW.COMMERCIALBIOTECHNOLOGY.COM

Journal of
COMMERCIAL
BIOTECHNOLOGY
http://CommercialBiotechnology.com

Journal of
COMMERCIAL BIOTECHNOLOGY

VOLUME 23 NUMBER 2 APRIL 2017

Contents

Article

Construction Engineering Management and its Assessment System Based on Green Building Methods

Yongxia Chen
is at the Civil Engineering College of NanJing, Forestory University, Nanjing, Jiangsu, China

ABSTRACT

In recent years, the construction industry has been searching for intra-industry development methods, developing new technologies as well as introducing new equipment and environment-friendly materials, etc., and the arising of green buildings has brought new opportunities to the development of construction industry. Therefore, this study was designed to analyze the engineering management system of green buildings, as well as explore the development mode, engineering design evaluation and construction management methods in the management of green buildings. The development of construction engineering is connected with the multiple relations among the government, developers and consumers. The government restrains behaviors of developers through policy control, thus to promote development activities. However, market promotion should be based on consumers' demand and purchase intension. Therefore, according to the game analysis between the government and developers, this study discussed the development management mechanism of construction engineering; combining with the development status of Chinese construction industry, four kinds of designing schemes of construction engineering were established, and the optimal scheme was selected according to the evaluation criteria of engineering construction products, thus to lower the construction costs; finally, based on the static game analysis of incomplete information of contractors, the choice mechanism of green construction contractors was put forward.

Journal of Commercial Biotechnology (2017) 23(2), 3–14. doi: 10.5912/jcb769
Keywords: Green building; evaluation system; game analysis; management mode

INTRODUCTION

A series of problems have occurred along with the development of construction industry, including abuse of resources, worsening of greenhouse effect and excessive deforestation, etc., which severely threatens our living environment; moreover, a host of facts indicate that the problems result from human construction activities[1]. As we all know, the energy consumption of construction industry and its related industries accounts for almost half of the energy consumption of national production[2–3].

Correspondence:
Yongxia Chen, Civil Engineering College of NanJing, Forestory University, Nanjing, China. E-mail: chenyongxia03@sina.com

The key of the problem is that, the energy consumption of unit building area of China is two to three times as much as that of developed countries[4–6]. With the acceleration of urbanization progress of China, the population that floats to cities every year reaches more than one hundred million, and tens of thousands of rural population settle in cities[7–8]. The migration of a large number of populations, especially the migration to large towns [9], has led to the continuous improvement of productive forces level; however, energy consumption, on the other hand, also increases rapidly[10–12].

Thus it can be seen that, resource shortage, energy tension and environmental degradation have become a great challenge that the Chinese construction industry faces at present, and arisen green construction design philosophy has been carried out aiming at energy saving and environmental protection. After years of effort,

the development of green construction is becoming more and more mature in China, indicating that, the consensus between development speed of China's modern economy and construction industry has been reached[13].

This study aimed to discuss theories of evaluation system of construction engineering, thus to put forward principles, steps and methods of establishing the evaluation system of green building; moreover, combining with the development status and experience of evaluation system of green construction engineering, reference values were provided for the construction and improvement of China's construction engineering management and the establishment of its evaluation system.

DEVELOPMENT AND MANAGEMENT MODE OF GREEN BUILDINGS

Analysis of Develop Market of Green Buildings

The development of green buildings involves in the multiple relations among government, developers and customers. Relevant policies are carried out by government for supervision, thus to further promote development activities of green buildings. However, the market of green buildings stimulates the development of green buildings mainly according to purchase intensions as well as demands of consumers.

The reason why government participates in the development process of green buildings is that, government plays its roles as the promoter, guider and supervisor in development of green buildings[14], indicating the capacity of service supporting of government.

Development Mode of Green Building Market

Principal-agent relation

From the perspective of politics, government is elected by consumers and consumers elect government to protect their legitimate interests[15–16]. In the process of development activities, government advertises to consumers to guide their consumption demand and direction; meanwhile, government also supervises behaviors of developers to guarantee rights and interests of consumers.

Relation of market supply and demand

Generally speaking, enterprises and consumers only have the relation of market supply and demand; consumers have the right of option and can choose their purchasing behaviors according to properties of products[17]. Market demand of products is relatively stable, which does not totally depend on price changes. As shown in figure 1, q_1 and q_2 refer to the minimal demand and the maximum demand in unit time of housing respectively. Therefore, the correlation between these two can be described by price-demand curves. In figure 1, the xx_1 curve refers to the demand curve of general merchandises, while the yy_1 and y_2y_3 curves refer to the demand curves of general buildings. The market mechanism can not adjust the resource allocation between consumers and enterprises under the circumstance that, the quality of products is poor and the price is very high. In this case, government regulation or administrative mechanism is vital.

Dynamic game refers to that, behaviors of participants are sequential, and the latter can observe the behavior state of the former before taking action[18]; the dynamic game problem of incomplete information can be found between government and developers.

The following assumptions were made:

- Monitoring cost of government is C_1 and examination probability is P_1;
- If developers give priority to long-term benefits, and opportunity cost is C_2, prestige benefit is R_1 and probability is P_2; on the contrary, if developers only value short-term benefits and employ trickery, costs of punishment and legal liability are C_3 and reputation loss is C_4.

One party of game is government, and the other one is developers; both parties of game only have bounded rationality and at least one party is incompletely rational. If two parties of game can not make the optimal decision immediately, they will experience a stage of learning, trial and error and imitation during repeated game, and with continuous adjustment, a dynamic balance can be achieved. During the game, government has two choices to answer to enterprises' decision on whether invest green buildings: carrying out incentive policies or not carrying out incentive policies. On the other hand, enterprises also have two choices to answer to the government's decision on whether implement incentive policies: invest construction of green buildings or invest construction of non-green buildings. Under the stimulation of government (probability is P_3), if developers invest green buildings (probability is P_4), the brought community income is τC_2 $(0 < \tau < 1)$; if government takes τC_2 as its own income, the loss of reputation is C_5; if developers

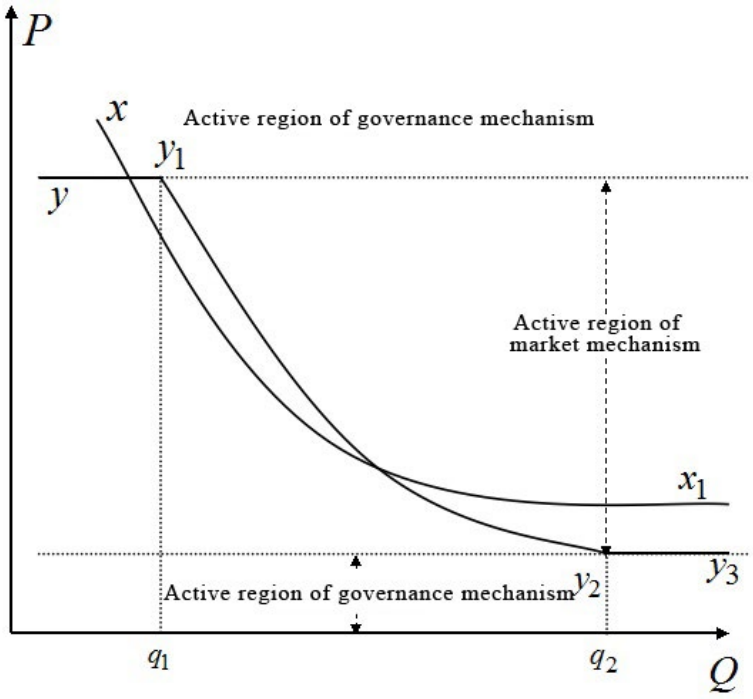


Figure 1: Demand curves of products

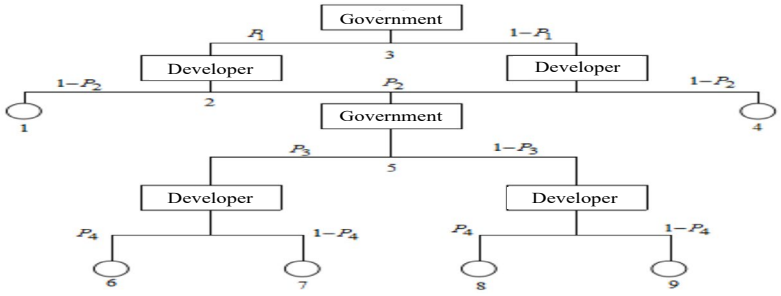


Figure 2: Game model between government and developers

invest non-green buildings, the fine after investigation of government is σC_3, $\sigma > 1$.

If developers carry out development activities of green buildings and government hand τC_2 and σC_3 over to the national treasury, the rewards are $k(\tau C_2 + C_3)$ and $(0 < k < 1)$.

If government does not monitor activities of developers properly, leading to collusion of developers and contractors, then the loss caused by dereliction of duty of government is C_6.

Thereby, the game model between government and developers is shown in figure 2.

Profit values of nodes are shown in table 1.

Model solution

Backward induction is adopted for seeking the equilibrium solution and the expected value of node 5 is:

$$\begin{aligned} E_{11}=&(\tau C_2-C_5-C_1)P_3P_4 \\ &+[k(\tau C_2+C_3)-C_1](1-P_3)P_4 \\ &+(\beta C_3-C_1-C_5)P_3(1-P_4) \\ &+(kC_3-C_1)(1-P_3)(1-P_4) \end{aligned} \tag{1}$$

$$\begin{aligned} E_{12}=&(\tau C_2-C_4)P_3P_4+(\beta C_3-C_4)P_3(1-P_4) \\ &-[\tau C_2+C_3+C_4](1-P_3)P_4 \\ &-(C_3+C_4)(1-P_3)(1-P_4) \end{aligned} \tag{2}$$

Table 1: Profit values of nodes

Node	Profit value
1	$-C_1, -C_2+R_1$
2	$(0, -C_2)$
3	(E_{21}, E_{22})
4	$(-C_6, 0)$
5	(E_{11}, E_{12})
6	$(\tau C_2-C_1-C_5, -\tau C_2-C_4)$
7	$(\sigma C_3-C_1-C_5, -\sigma C_3-C_4)$
8	$(k(\tau C_2+C_3)-C_1, -\tau C_2-C_3-C_4)$
9	$(kC_3-C_1, -C_3-C_4)$

Notes: E_{11}, E_{12}, E_{21} and E_{22} refer to expected profit values under different states; details are as follows.

Solution procedures of nash equilibrium of above two equations are:

$$\frac{\partial E_{11}}{\partial P_3}=(\tau C_2-C_5-C_1)P_4+(\sigma C_3-C_1-C_5)(1-P_4) -[k(\tau C_2+C_3)-C_1]P_4 -(kC_3-C_1)(1-P_4)=0 \quad (3)$$

$$\frac{\partial E_{12}}{\partial P_4}=P_3(\tau C_2-C_4)-(\sigma C_3-C_4)P_3 +[-\tau C_2-C_3-C_4](1-P_3) +(C_3+C_4)(1-P_3)=0 \quad (4)$$

$$P_3^*=\frac{\tau C_2}{\sigma C_3}, P_4^*=\frac{(k-\sigma)C_3+C_5}{(1-k)\tau C_2-\beta C_3} \quad (5)$$

Thus (P_3^*, P_4^*) are substituted into equation (1) and (2):

$$E_{11}^*=P_4^* k\tau C_2+kC_3-C_1 \quad (6)$$

$$E_{12}^*=\frac{\tau C_2}{\sigma}-\tau C_2-C_3-C_4 \quad (7)$$

After that, calculation procedures of the expected value of node 3 are:

$$E_{21}=P_1P_2(-C_1)+P_1(1-P_2)E_{11}^*-C_6(1-P_1)(1-P_2) \quad (8)$$

$$E_{21}=P_1P_2(-C_1)+P_1(1-P_2)E_{11}^*-C_6(1-P_1)(1-P_2) \quad (9)$$

Similarly,

$$\frac{\partial E_{21}}{\partial P_1}=P_2(-C_1)+(1-P_2)E_{11}^*+C_6(1-P_2)=0 \quad (10)$$

Solution of equation (10) is:

$$P_1^*=\frac{C_2}{R_1-E_{12}^*}, P_2^*=1-\frac{C_1}{C_1+E_{11}^*+C_6} \quad (11)$$

Results analysis

1. The probability of government regulation is related to benefits from development of qualified green buildings and the expected values[19]; the higher the value of C_2, the bigger the value of P_1^* (probability of government regulation); the bigger the value of R_1 (benefits from protection of green building reputation by developers) and E_{12}^*, the higher the enthusiasm of developers developing qualified green buildings and the smaller the value of P_1^*.
2. The higher the C_1 (costs of government regulation), the smaller the P_2^*. The bigger the E_{11}^* (benefits of government in the first stage), the bigger the P_2^*; however, the bigger the C_6 (loss of government reputation) is, the bigger the P_2^* will be.
3. The probability of government stimulating developers is related to following factors: bigger α leads to higher τC_2 (social benefits) and bigger P_3^*; the bigger the σ is, the higher the fine σC_3 is; if developers respect justice and abide by the laws to avoid fine, the P_3^* reduces.
4. The probability P_4^* of developers developing green buildings is related to following factors: if the incentive bonus given by government is not in direct proportion to the extra money paid by developers during development of green buildings, developers are more inclined to invest unqualified green buildings, resulting in rent-seeking behaviors of developers and contractors, and P_4^* becomes smaller.

Although the determination of game equilibrium is difficult, or it is hard to determine its math expression, it does not mean that game model is meaningless; game model well explains some phenomena in implementation process of constructional engineering.

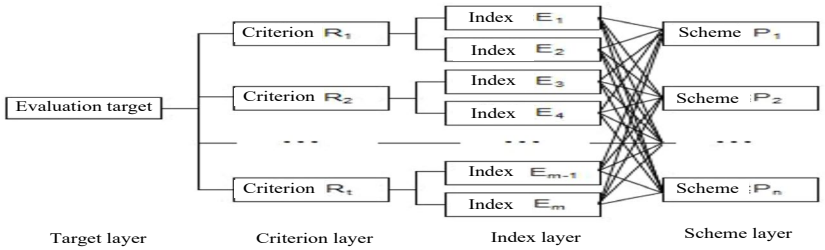


Figure 3: Hierarchical analysis structural model

Therefore, in the develop market of green buildings, participants in game should cooperate with each other and strictly perform their own duties, so as to establish the information sharing mechanism. Thus, an improved incentive and punishment fiscal policy system should be established; the tax system and green building labeling system that are related to green buildings should be improved; the service mechanism of green buildings should be perfected.

COMPREHENSIVE EVALUATION SYSTEM OF DESIGN SCHEME OF GREEN BUILDINGS AND APPLICATION EXAMPLES

Mathematical Methods of Constructing Evaluation Index System

Evaluation feature set is composed of comprehensive evaluation of all relevant factors of something, and evaluation index set is composed of a series of indexes applied to the evaluation of the thing. Systematization of evaluation index set to evaluation index system requires analytic hierarchy process (AHP). Generally speaking, it should be decomposed to appropriate hierarchies according to characteristics of the evaluation object, thus to obtain a clear and simple analytic hierarchy structure chart (figure 3).

Comprehensive evaluation indexes of green building design scheme are final results obtained after evaluation, which are evaluation targets. The integral level of green building design scheme can be reflected by system evaluation and comparison, and the measuring results come from four evaluation criteria of the criterion layer.

Digitization of Examples of Green Building Engineering

An office building with floor space of 5578.2 m^2 was selected as the research object in this study with a total investment of more than 32 million China Yuan (CNY) of total investment. Firstly, according to essential characteristics of the project, this study proposed four architectural design schemes, and relevant evaluation index data of four design schemes were acquired. Detailed data are shown in table 2.

Scoring and Calculation of Evaluation Indexes

In this study, the first-grade evaluation indexes were selected as the comprehensive evaluation indexes of construction engineering design schemes. Evaluation scores of the first-grade indexes were obtained by comprehensively evaluating the second-grade evaluation indexes according to evaluation criteria of the second-grade indexes.

The index of heating and air-conditioning system is the sum of energy consumption of yearly heating, cooling and heat supply, namely, yearly energy consumption measurement of building heating and air-conditioning system. The specific value of total amount of yearly energy consumption of the heating and air-conditioning system and area of structure is the yearly energy consumption of the heating and air-conditioning system. The computational formula is $Q_c = M_t/S$. In the formula, Q_c refers to yearly energy consumption (kWh/m^2) of the heating and air-conditioning system; M_t refers to the yearly gross energy consumption (kWh) of the heating and air-conditioning system; S refers to the area of building (m^2).

Quantitative evaluation of the energy consumption of the heating and air-conditioning system inside the building was taken as an example, as shown in table 3.

Table 2: Evaluation index values of four schemes

Target layer	Criterion layer	First-grade evaluation index	Second-grade evaluation index	Scheme 1	Scheme 2	Scheme 3	Scheme 4
Comprehensive evaluation of green building design scheme	Economical criterion R_1	Life cycle cost E_{11}	Construction cost (ten thousand CNY)	3200	3011	2872	2686
			Operation and maintenance cost during life cycle (ten thousand CNY)	2686	2976	3382	3478
		Increment economic benefit E_{12}	Payback time of investment (year)	9	7	7	6
			Net present value of investment (ten thousand CNY)	803	551	138	47
	Criterion R_2 of resource utilization and environment protection	Land saving and outdoor environment E_{21}	Volume fraction (%)	3.2	3.1	3.4	3.6
			Usage rate of new-type material for wall (%)	43	40	35	39
			Land utilization rate (%)	77	81	75	74
			Greening rate (%)	55	55	53	53
			Convenience of public transportation	8	8	7	6
			Perfect rate of auxiliary facilities	9	9	8	8
			Area of underground public architecture (m^2)	1122	1234	990	1025
		Energy conservation and resource utilization E_{22}	Shape coefficient of architecture (l/m)	0.30	0.31	0.36	0.39
			Thermal performance of maintenance structure (W/m^2,K)	0.6	0.8	1.1	1.2
			Energy consumption of illuminating system (W/m^2)	3.1	3.5	4.0	4.0
			Energy consumption of heating and air-conditioning system (kWh/m^2)	76	88	105	113
		Water saving and water resource utilization E_{23}	Use ratio of recycled water (%)	18	17	14	15
			Use ratio of rainwater (%)	15	16	12	12
			Water saving instrument and tube efficiency (%)	4.8	4.5	4.2	4.3

Table 2: Continued

Target layer	Criterion layer	First-grade evaluation index	Second-grade evaluation index	Scheme 1	Scheme 2	Scheme 3	Scheme 4
		Material saving and material resources utilization E_{24}	Design of material saving measures	8	8	7	7
			Recovery rate of building materials (%)	8	9	11	12
			Use ratio of recyclable material (%)	25	27	25	24
		Indoor environmental quality E_{25}	Structural rationality	9	8	7	6
			Indoor sunlight	8	9	8	6
			Daylight factor (%)	5	6	4	4
			Natural ventilation	9	8	7	8
			Effect of sound insulation and noise reduction measures	9	9	8	8
			Internal and external sunshade measure	8	8	7	7
	Technique and management criterion R_3	Technology application E_{31}	Difficulty of construction technique	6	6	8	9
			Design of transitive persistence	9	8	8	7
		Building management level E_{32}	Time limit for project construction	1.3	1.3	1.2	1.1
			Organization structure and management process of the project	7	7	8	9
	Social development influence R_4	Social development influence E_{41}	Green building technology and product promotion rate	8	9	8	7
			Energy consumption of gross value of production of unit building (Mtce/ ten thousand CNY)	0.62	0.69	0.81	0.84
		Regional development influence E_{42}	Cultural environment protection	7	8	7	6
			Harmony between architectural style and overall planning of the region	9	7	7	7
			Activation of regional culture	7	7	6	7

Comparison and scoring method was adopted to determine weight of the second-grade evaluation indexes; during the process, project decision maker could adjust index weight according to requirements of design functions, as shown in table 4.

It is a key problem of choosing a method to weight evaluation indexes, because during the comprehensive evaluation of multi-index architectural design schemes, selection of appropriate weight calculation method is the basis of comprehensively evaluating whether the index system can complete quantitative evaluation or not. Weight calculation is directly related to the scientificity and accuracy comprehensive evaluation.

Weight coefficients of second-grade evaluation indexes are obtained by the weight coefficient of single index divided by weight value. Then scores of the first-grade evaluation indexes can be obtained for project evaluation by addition of calculated index scores. The scoring calculation of energy saving and resource usage index was taken as an example, as shown in table 5.

According to above scoring methods, score values of evaluation indexes of the four design schemes of green building are shown in table 6.

Comprehensive Evaluation of Green Building Design Schemes using Distance Evaluation Technique

In the theory of information, entropy reflects the disordering degree of information; the smaller the entropy, the smaller the disordering degree of system[20–21].

Table 3: Evaluation of energy consumption of heating and air-conditioning system

Score	Evaluation	Yearly energy consumption of heating and air-conditioning system (kWh/m^2)	
		Yearly energy consumption of heating system (kWh/m^2)	Yearly energy consumption of air-conditioning system (kWh/m^2)
5	Pass	≤85	≤75
6	Average	≤75	≤65
7	Good	≤65	≤55
8	Very good	≤55	≤45
9	Highly good	≤45	≤35
10	Excellent	≤35	≤25

Table 6: Score values of evaluation indexes of the four design schemes

Index	P_1	P_2	P_3	P_4
E_1	7.5	7.2	6.9	7.0
E_2	8.0	8.1	7.8	7.7
E_3	8.3	8.1	7.9	7.5
E_4	8.4	8.1	7.9	7.4
E_5	7.3	7.0	6.7	6.7
E_6	6.7	6.7	7.2	7.1
E_7	8.4	8.1	8.1	7.7
E_8	8.3	8.6	9.2	9.2
E_9	7.4	7.5	8.0	8.0
E_{10}	8.3	6.2	8.2	7.9
E_{11}	7.3	6.9	6.9	6.6

Table 4: Weight values of the second-grade evaluation indexes

Grade	5	6	7	8	9	10
Relative importance	Not important at all	Significantly minor	Very minor	Minor	A little bit minor	Equal importance

Note: The most important target was taken as the reference for above data.

Table 5: Scoring of the first-grade evaluation indexes

Index	Weight value	Weight coefficient	Score	Index score
Building shape coefficient	9	0.25	9	2.13
Thermal performance of building envelope	8	0.27	7	1.82
Energy consumption of heating and air-conditioning system	10	0.28	7	2.38
Energy consumption of illuminating system	8	0.20	8	1.64
General comment: energy saving and resource usage	35	1	31	7.97

Proximity

Assume P is the set of n (in this study, n=4) green building schemes and E is the set of m (in this study, m=11) evaluation indexes; $P = \{P_1, P_2, P_3, P_4\}$ and $E=\{E_1, E_2, \cdots, E_{11}\}$. $i \in N$, $j \in M$, $N=\{1,2,\cdots,n\}$ and $M=\{1,2,\cdots,m\}$. Suppose y_{ij} is the attribute value of scheme P_i to evaluation index E_j, thus the decision matrix Y of P based on E according to methods of evaluation model can be constructed:

$$Y=\begin{bmatrix} y_{11} & \cdots & y_{1m} \\ \vdots & \ddots & \vdots \\ y_{n1} & \cdots & y_{nm} \end{bmatrix} = \begin{bmatrix} 7.5 & 8.0 & 8.3 & 8.4 & 7.3 & 6.7 & 8.4 & 8.3 & 7.4 & 8.3 & 7.3 \\ 7.2 & 8.1 & 8.1 & 8.1 & 7.0 & 6.7 & 8.1 & 8.6 & 7.5 & 8.2 & 6.9 \\ 6.9 & 7.8 & 7.9 & 7.9 & 6.7 & 7.2 & 8.1 & 9.2 & 8.0 & 8.2 & 6.9 \\ 7.0 & 7.7 & 7.5 & 7.5 & 6.7 & 7.1 & 7.7 & 9.2 & 8.0 & 7.9 & 6.6 \end{bmatrix} \quad (12)$$

Suppose y_{ik} is the calculation value of evaluation index E_k of alternative scheme P_i, $y_k^* = \max\{y_k\}$ is the ideal value of evaluation index E_k. It can be known from Y that, scheme 1 has the lowest cost of life cycle and the highest evaluation index scores, and its ideal value $y_1^* = 7.5$. Calculation of the proximity $d_k = y_{ik}/y_k^*$ of calculation value and ideal value is:

Scheme 1: $d_{11}=\frac{y_{11}}{y_1^*}=\frac{7.5}{7.5}=1$ Scheme 2: $d_{21}=\frac{y_{21}}{y_1^*}=\frac{7.2}{7.5}=0.960$

Scheme 1: $d_{31}=\frac{y_{31}}{y_1^*}=\frac{6.9}{7.5}=0.920$ Scheme 2:

$$d_{41}=\frac{y_{41}}{y_1^*}=\frac{7.0}{7.5}=0.933$$

Constructed proximity matrix is:

$$d=\begin{bmatrix} d_{11} & \cdots & d_{1m} \\ \vdots & \ddots & \vdots \\ d_{n1} & \cdots & d_{nm} \end{bmatrix} \quad (13)$$

Weight coefficients of indexes

Entropy evaluation method was used to determine weight coefficients of indexes. Firstly, index value weight of the i^{th} scheme under the j^{th} evaluation index is calculated:

$$\rho_{ij}=\frac{y_{ij}}{\sum_{i=1}^{n} y_{ij}} \quad (14)$$

In equation (14), $i=1,2,\cdots,n$; $j=1,2,\cdots,m$, thus:

$$\rho_{11}=\frac{7.5}{7.5+7.2+6.9+7.0}=0.262$$

$$\rho_{21}=\frac{7.2}{7.5+7.2+6.9+7.0}=0.253$$

$$\rho_{31}=\frac{6.9}{7.5+7.2+6.9+7.0}=0.242$$

$$\rho_{41}=\frac{7.0}{7.5+7.2+6.9+7.0}=0.246$$

Secondly, the relative entropy of the j^{th} evaluation index is calculated:

$$e_j=-\lambda\sum_{i=1}^{n}\rho_{ij}\cdot\ln\rho_{ij} \quad (15)$$

In equation (15), $\lambda = 1/\ln m$, thus:

$$e_1=-\frac{1}{\ln 4}\sum_{i=1}^{n}\rho_{ij}\cdot\ln\rho_{ij}$$
$$=-\frac{1}{\ln 4}[0.262\times\ln(0.262)+0.253\times\ln(0.253)$$
$$+0.242\times\ln(0.242)+0.246\times\ln(0.246)]$$
$$=0.99998$$

Similarly, relative entropies of other evaluation indexes are calculated, as shown in table 7:

Entropy weight of the j^{th} evaluation index is:

$$w_j=\frac{1-e_j}{\sum_{j=1}^{m}(1-e_j)}=\frac{1-e_j}{11-\sum_{j=1}^{m}e_j} \quad (16)$$

And $\sum_{j=1}^{m} w_j=1$.

Thus entropy weights of evaluation indexes are shown in table 8.

Finally, the weighted sum S_i of the range distance between ideal indexes and evaluation indexes of the four schemes is calculated according to the following equation:

$$S_i=\sum_{j=1}^{m}\beta_j(1-d_{ij}) \quad (17)$$

Table 7: Relative entropies of evaluation indexes

	E_1	E_2	E_3	E_4	E_5	E_6
e_j	0.99998	0.99989	0.99992	0.99938	0.99991	0.99991
	E_7	E_8	E_9	E_{10}	E_{11}	-
e_j	0.99993	0.99994	0.99990	0.99988	0.99979	-

Table 8: Entropy weights of evaluation indexes

	E_1	E_2	E_3	E_4	E_5	E_6	E_7	E_8	E_9	E_{10}	E_{10}
W_j	0.089	0.048	0.091	0.140	0.101	0.101	0.049	0.192	0.129	0.017	0.066

Therefore, distance values S_i between four schemes and the ideal scheme are:

S_i = (0.0414 0.0209 0.0465 0.0413)

Small S_i means the distance between the design scheme and the ideal scheme is small, thus the design scheme is good. Results show that $S_3 > S_1 > S_4 > S_2$, thus scheme 2 is the optimal scheme.

After the establishment of design scheme, the construction stage starts. Construction and management stage of green buildings is evaluated and analyzed next.

CONSTRUCTION MANAGEMENT OF GREEN BUILDINGS

Selection of the Contractor

Mechanism design theory is a branch of economics and a kind of special incomplete information countermeasure, and its core is to design game rules to achieve certain goals. In such kind of countermeasure, there is one tenderee and one or multiple tenderers[22]. The tendering processes among tenderers can be taken as simultaneous incomplete information static game[23].

Player

Players refer to immediate parties participated in the game. In the game model of construction project bidding, there is one buyer and multiple sellers (including suppliers and contractors); suppose the buyer selects the contractor by open tendering; thus for convenience, suppose the construction cost of each tenderee independently complies with uniform distribution on [0, 1]. Suppose there are n contractors and individual cost of the i[th] contractor to the construction engineering is C_i, $i=1,2,\cdots,n$; B_i refers to the offer of the i[th] contractor; if the contractor wins the bidding, his obtained net benefit is B_i-C_i, otherwise, the benefit is 0.

Payoff function

If project schemes of all tenderees meet the requirements of bid inviting, the contractor with the lowest offer can acquire the contract to build. Thus the payoff function of the i[th] contractor is:

$$U_i(B_i,B_j,C_i)=\begin{cases}B_i-C_i & ,B_i<B_j\\ 0 & ,B_i>B_j\end{cases} \quad (18)$$

$i,j=1,2,\cdots,n$; $i\neq j$.

Bidding strategy

The offer $B_i(C_i)$ of the tenderee i is a strict monotone increasing function of its individual costs. Suppose the player has symmetry, then the optimal policy functions of every tenderee are the same, except for their individual costs. Therefore, the optimized quotation of tenderees with high individual costs is strictly higher than that of tenderees with low individual costs.

Because the game is symmetrical, only the symmetrical equilibrium bidding strategy $B = B^*(C)$ is taken into consideration. On this equilibrium point, every bid can achieve the maximization of its self interest, whether a successful bidder or not.

Modeling and equilibrium analysis

Suppose the individual cost of tenderer i is C and his tender offer is B, thus his expected value of pay is:

$$U_i=(B-C)\prod_{i\neq j}P(B<B_j) \quad (19)$$

In equation (19), $P(B < B_j)$ is the probability of $B < B_j$; B_j refers to the offer of contractor j and $(B\text{-}C)$ is the net benefit of successful bidder. If the strategic function $B^*(C)$ is the strictly increasing function of C and is continuously differentiable, thus the inverse function of continuously differentiable strategic function is $C^*=\Phi(B)$. Offer of other tenderer j being bigger than B equals to its construction cost $C_j>\Phi(B)$; because costs of tenderer distributes evenly in [0, 1], thus:

$$P(B<B_j)=P[\Phi(B)<C_j]=1-\Phi(B) \quad (20)$$

According to properties of uniform distribution,

$$\prod P(B<B_j)=[1-\Phi(B)]^{n-1} \quad (21)$$

At present, the problem of tenderer i is the utility maximization, i.e.,

$$MaxU_i=(B-C)\prod_{i\neq j}P(B<B_j)[1-\Phi(B)]^{n-1} \quad (22)$$

The first-order optimality condition is:

$$[1-\Phi(B)]^{n-1}-(B-C)(n-1)[1-\Phi(B)]^{n-2}\Phi(B)=0$$

According to $\Phi(B)=C$ and $\Phi(B)=\frac{\partial C}{\partial B}$,

$(1-C)^{n-1}\partial B-(B-C)(n-1)(1-C)^{n-2}\partial C=0$.

The optimal bidding strategy is:

$$B^*(C)=\frac{1}{n}+\frac{n-1}{n}C \quad (23)$$

In equation (23), when $n\to\infty$, $B\to C$; the difference between the optimal offer and the real cost of tenderer after further observation is:

$$B^*(C)-C=\frac{1}{n}+\frac{n-1}{n}C-C=\frac{1-C}{n}$$

Therefore, enlargement of bidding scale can narrow the distance and the optimal offer can truly reflect the construct cost of tenderer.

However, in practical work, the cost expenditure, technical condition and marginal effect can become main influencing factors of bidding[24]. From the aspect of marginal effect, the marginal effect MB of bid inviting decreases with the increase of the number of bidders (n). On the contrary, the marginal cost MC increases with the increase of n. When MB=MC, suppose the number of bidders is n* and the project costs ten million Chinese Yuan, then according to the quadratic regression analysis of n* and bidding scale (suppose the scale is S), n*=3.24+0.0015S-1.31×10-7S2.

Therefore, for a constructional engineering that costs ten million Chinese Yuan, five tenderers should be chosen.

Planning and Management of Construction Organization

Construction management of green buildings includes five aspects: organization management, planning management, implementation management, evaluation management and human security and health management[25]. Green construction schemes should include environmental protection measures, material saving measures, energy saving measures, construction energy saving planning, target determination, formulation of energy saving measures and land saving and construction land protection measures, which should form an independent chapter and be examined and approved according to relevant provisions. Construction schemes should not be determined only based on cost control; during the process of construction, protection of surrounding environment should be given priority to.

CONCLUSION

Following conclusions are drawn in this study:

1. The development of construction engineering is connected with the multiple relations among government, developers and consumers. The selection of contractors of green buildings is mainly based on the mechanism design theory, and its core is designing game rules to achieve specific purposes. In order to achieve this, designers will design specific rule structures, thus the performers can operate following the game rules automatically. The selection of contractors of green buildings is an incomplete information static game. Relevant models are constructed according to government functions and bidding strategies; the equilibrium analysis is carried out and relevant conclusions are obtained.
2. After a comprehensive evaluation of four green building design schemes, principles and strategies of the index system construction are put forward. First of all, the standard evaluation methods of the second evaluation indexes are introduced through examples. Then based on this, the standard methods of calculating the first evaluation indexes are introduced. Finally a comprehensive evaluation index system of green building design schemes is established.
3. During the construction of green buildings, green requirements like energy saving and emission reduction should be met; moreover, a selection mechanism of green building contractors is established according to the incomplete information static game model.

REFERENCES

1. Araszkiewicz, K. (2016) Green BIM concept-scandinavian inspirations. *Archives of Civil Engineering* 62(1): 99–110.
2. Medineckiene, M., Zavadskas, E.K., and Björk, F. et al. (2014) Multi-criteria decision-making system for sustainable building assessment/certification. *Archives of Civil & Mechanical Engineering* 15(1): 11–18.
3. Chan, I., Leung, M. (2012) Managing Stress of Hong Kong expatriate construction professionals in Mainland China: A focus group studies to exploring individual coping strategies and organizational support. *Journal*

of Construction Engineering & Management 138: 1150–1160.

4. Prakash, D., Ravikumar, P. (2013) Transient analysis of heat transfer across the residential building roof with Pcm and wood wool - A case study by numerical simulation approach. *Archives of Civil Engineering* LIX(4): 483–497.
5. Xu, Y., Chan, A.P.C., and Yeung, J.F.Y. (2015) Developing a fuzzy risk allocation model for PPP projects in China. *Journal of Construction Engineering & Management* 136(8): 894–903.
6. Shen, Z., Jensen, W. Berryman, C. et al. (2010) Comparative study of activity-based construction labor productivity in the United States and China. *Journal of Management in Engineering* 27(2): 116–124.
7. Wang, S., Wahab, M.I.M., and Fang, L. (2011) Managing construction risks of ap1000 nuclear power plants in china. *Journal of Systems Science & Systems Engineering* 20(1): 43–69.
8. Martek, I., Chen, C. (2015) Localization typologies evident among foreign enterprises active in the Chinese construction market. *Journal of Construction Engineering & Management* 139(10): 5971–5984.
9. Konior, J. (2015) Random and fuzzy measure of unpredictable construction works. *Archives of Civil Engineering* 61(3): 75–88.
10. Kowal, Z., Siedlecka, M., Piotrowski, R. et al. (2015) Shapes of energy-active segments of steel buildings. *Archives of Civil Engineering* 61(3): 119–132.
11. Sun, W.Z., and Zhou, G.Q. (2010) KPIs: Analyzing the impact of building information modeling on construction industry in China[C]// Industrial Engineering and Engineering Management (IE&EM), 2010 IEEE 17Th International Conference on. 311-315.
12. Xu, C.H., and Huang, J.J. (2014) Research on manufacturing engineering in agriculture with construction of China's rural logistics system. *Applied Mechanics & Materials* 540: 532–536.
13. Zhang, Z.R., Yang, R.S., and Zhao, L. et al. (2011) Study on fast estimation method of mine construction engineering cost. *Energy Procedia* 13: 2811–2817.
14. Sousa, J., Bragança, L., and Almeida, M. et al. (2013) Research on the Portuguese building stock and its impacts on energy consumption – An average U-value approach. *Archives of Civil Engineering* 59(4): 523–546.
15. Howell, G. A., Ballard, G., and Tommelein, I. (2014) Construction Engineering—Reinvigorating the Discipline. *Journal of Construction Engineering & Management* 137(10): 740–744.
16. Howell, G.A., Ballard, G., and Tommelein, I. (2010) CEC Construction engineering—reinvigorating the discipline. *Journal of Construction Engineering & Management* 137(10): 740–744.
17. Tan, W.F., and Zhang, B. (2011) Research on R&D cooperation of petrochemical enterprise based on game theory. *Applied Mechanics & Materials* 71–78: 2257–2261.
18. Chen, X., and Liu, X. (2015) Influence of transaction cost on developer's decision of developing green building. *Journal of Tongji University* 43(1): 153–159.
19. Wang, F.C. and Song, W. (2015) Effects of crumb rubber on compressive strength of cement-treated soil. *Archives of Civil Engineering* 61(4): 59–78.
20. Guo, G., and Wang, Z. (2010) Dynamic Game Analysis in Program Emergency Management of Engineering Construction Company[C]// International Conference on E-Business and E-Government. IEEE, 2688–2691, 2010.
21. Schexnayder, C., and Anderson, S. (2011) Construction engineering education: History and challenge. *Journal of Construction Engineering & Management* 137(10): 730–739.
22. Shao, H., and Fu, H. (2015) Construction Engineering Project Quality Evaluation Method Based on Fuzzy Analytic Hierarchy Process[C]// 2015 International Conference on Intelligent Transportation, Big Data & Smart City (ICITBS). *IEEE Computer Society*, 228–231.
23. Xi, W. (2014) Construction engineering quality reflected in financial information and model establishment[C]// International Conference on Service Systems and Service Management. 1–4, 2014.
24. De, l.G.J.M. Updates to Journal of Construction Engineering and Management Editorial Board. *Journal of Construction Engineering & Management* 139(5): 457–458.
25. Tamošaitiene, J. (2016) Game theory applications in construction engineering and management. *Ukio Technologinis Ir Ekonominis Vystymas* 16(2): 16.

Article

Early Assessment of Medical Devices in Development for Company Decision Making: An Exploration of Best Practices

Katarzyna Markiewicz
is at the Department of Health Technology and Services Research, University of Twente, MIRA institute for Biomedical Technology and Technical Medicine, The Netherlands.

Janine van Til
is Assistant Professor, Department of Health Technology and Services Research, University of Twente, MIRA institute for Biomedical Technology and Technical Medicine, The Netherlands.

Maarten IJzerman
is Professor (m.j.ijzerman@utwente.nl), Department of Health Technology and Services Research, University of Twente, MIRA institute for Biomedical Technology and Technical Medicine, The Netherlands.

ABSTRACT

To improve successful development and clinical use of medical technologies, it is suggested that manufacturers should start collecting evidence on devices effectiveness and efficiency early in their development. The aim of this study was to explore whether and how Dutch manufacturers perform an early assessment of medical devices through semi-structured interviews with key-informants from medical device companies. The primary focus was to identify why, how and to what degree these informants were engaged in early assessment activities to analyse the clinical context, the market, potential stakeholders, and the financial and health economic impact of their medical device. 37 interviews were performed with key-informants of 36 companies. The majority (N=19) of the companies are using internal resources and external consultants to perform early assessment activities. Typically, the assessment activities starts at the idea generation stage, and lasts until the post-marketing surveillance. The least developed areas of the assessment are health economic evaluation from the society perspective and formal stakeholders' analysis. Many methods seem to be in use to assess medical devices, however, there is no clear understanding of how they should be used, what evidence manufacturers could gather with their use, and how they influence the decision-making process within the companies.

Journal of Commercial Biotechnology (2017) 23(2), 15–30. doi: 10.5912/jcb780
Keywords: healthcare economics, health technology assessment, cost-effectiveness analysis; medical devices; new product development

INTRODUCTION

Medical devices play a crucial role in the continuing advancement of healthcare, providing new solutions that challenge existing paradigms and revolutionize the way treatments are administered[1-3]. The medical devices industry is now seen as one of the fastest growing ones, with the technological advances driven by an increasingly demanding market with growing patient population and legislative requirements, amplifying health policy reforms, and tough quality and regulatory hurdles[4-8]. A multitude of medical devices appears on the market every year, where medical devices are defined by the European Commission as "any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be

Correspondence:
Katarzyna Markiewicz, University of Twente. Email:
katarzyna.b.markiewicz@gmail.com

used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings"[9].

To enter the market, a device manufacturer must demonstrate that it is safe, that it produces value to patients and society at a reasonable cost, that it has potential to bring significant savings to the healthcare system, and that the risks associated with its use are acceptable when weighed against the benefits to patients[7]. Health Technology Assessment (HTA) is the scientific discipline to systematically collect evidence on the effects, risks and health economic consequences of new medical technologies[10]. Over the past decades, it has been difficult for small and medium sized companies (SMEs), that constitute around 75 percent of the medical device industry, to implement HTA in their business process[5]. Those SMEs operate under constant financial pressure[1,5,11].

However, although HTA is not a core activity in most SMEs it is expected to become more important in the near future. A recent Dutch report reflects on the need for generating clinical evidence on safety and efficacy before market launch of medical devices, as do other policy documents such as the recently revised regulations in the EU urging for collection of clinical evidence throughout the market lifetime of a device[12,13]. All these developments witness the current debate on safety of medical devices and the problems identified in the current regulatory framework.

So far, knowledge on HTA in SMEs is limited. In 2012, Craven et al.[14] explored the levels of health economics knowledge within English SMEs. The results revealed that 60 percent of SMEs representatives had low or no HTA experience. Clinical trials and cost analyses or cost-effectiveness studies were the most highly cited means by which SMEs aim to demonstrate value of medical devices to the purchasers. However, those methods were reported as having no formal influence on the decision-making process within SMEs.

Ideally, HTA should be conducted as early as possible in the device development process[15-17]. That way the development can either emerge or be stopped without major financial drawbacks for the company. The requirements of the stakeholders should constitute a base for an assessment and can be used to prioritize the development of medical devices most likely to succeed among others. At the same time, medical device manufacturers could use the early evidence gathered to enhance the efficiency of the use of research and development (R&D) resources within the company[15,16,18].

This aim of this study was to analyse whether and how medical devices manufacturers in the Netherlands perform an early assessment of medical devices that would allow them to meet the requirements of potential stakeholders. The Dutch medical device industry market was chosen, because of the large amount of public-private partnerships present in that market, e.g. The Centre for Translational Molecular Medicine (CTMM).

METHODS

Exploration of Early HTA Assessment Methodologies in Selected Companies

Four areas of an early assessment of the medical devices were subject of this study and incorporated in the

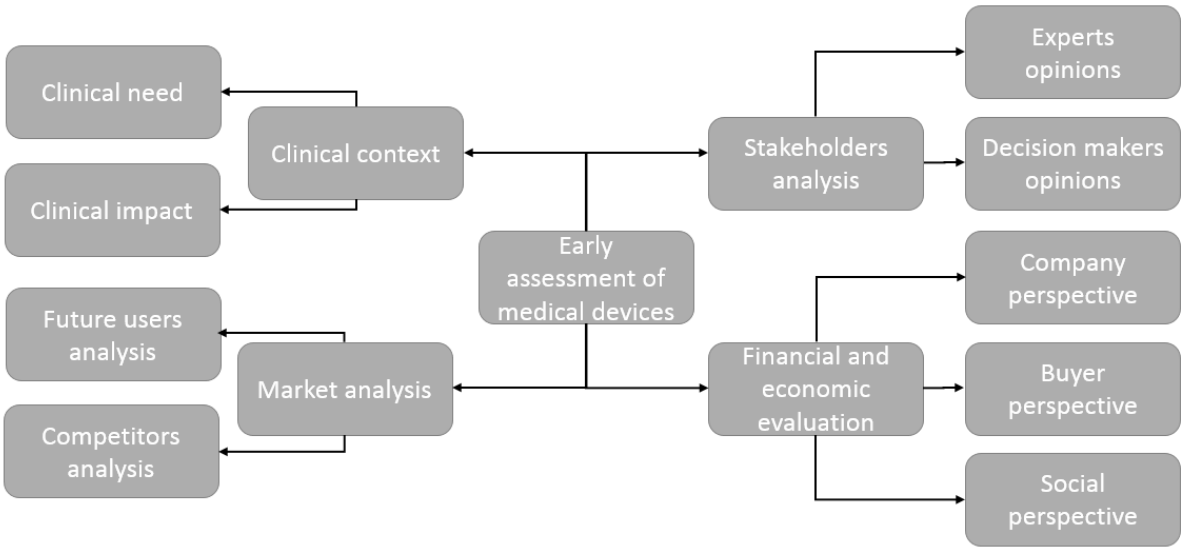


Figure 1: The areas of an early assessment of medical devices as distinguished in this research.

structured interviews: (1) analysis of the clinical context of medical device use; (2) market analysis; (3) stakeholders analysis; and (4) financial and health economic evaluation of new medical device. In addition, the interviews were held so that a better understanding of the specific role of early assessments in companies could be elaborated. A detailed map of the four topics for early assessment as well as the specific elements is provided in figure 1.

The analysis of the clinical context of medical device included the criteria used by the companies to evaluate clinical impact and the clinical need for the novel medical device, e.g. the underlying disease state and disease severity. The market analysis as a part of an early assessment in this research was assumed to be based on the analysis of main competitors and the analysis of the future users. The stakeholders' analysis was assumed to be based on the opinions of the experts, and the opinions of the decision makers. Finally, in the financial and health economic methods the company financial prospects as well as the buyer and societal perspective were analyzed. The list of methods presented during the interviews was extracted from the literature, and it was complemented during the validation of the interviews, and during the interviews themselves, as participants were asked to add methods if they thought any were missing. In general, specific methodologies (e.g. the Headroom method) were not explicitly included, as some of them might not be familiar to the medical device companies employees, so short description of the practical aims and results of those methods were used instead. During the interviews participants were asked to select those methods from the list which are being used in the company to assess medical device. Finally, the participants were asked to indicate at which stage the company started and finished specific assessments as well as which assessments were carried out iteratively throughout the development cycle. Six roughly defined medical device development stages were: (1) idea generation; (2) before prototype development starts; (3) during the prototyping; (4) gathering evidence on device effectiveness and efficiency; (5) device marketing; and (6) post-marketing surveillance.

Interview Design and Selection of Participants

This research was based on semi-structured face-to-face interviews with key-informants within medical device companies in the Netherlands. "Key-informants" in this study were defined as those people within the medical device companies who have experience-based and/or professional-based knowledge on different aspects of the medical device development and/or implementation, e.g. assessment practices, regulatory access, reimbursement[19].

After designing the interview format, all questions were pilot tested by experienced representatives in academic science and in the medical device industry, based in the Netherlands (3 people), and in the United Kingdom (1 person). The objective of the validation was to make sure that the questions covered the full range of methods and that the content of the questions will be easily understandable to the key-informants, i.e. in case of no scientific background in the early assessment of medical devices topic.

The participants of this study were selected with the use of the convenience sample method, based on the structured search of biomedical companies online. In total 91 companies were selected. The Chief Executive Officers (CEOs), or Managers within the topic of interest, of those companies were identified with the use of LinkedIn service and contacted via the telephone, with the use of the number provided on the companies websites. During the phone conversation the CEOs were first introduced to the research topic and asked about the willingness of their company to participate in the study. After the approval of the CEOs, the researchers scheduled the face to face structured interview with the CEOs themselves, or contacted the person indicated by the CEOs as the key-informant. In total 36 CEOs were interested in the participation, with one large company indicating two people from two different departments as key-informants for the interviews. 37 face-to-face structured interviews were conducted. Before the interviews, the interviewer explained the purpose and format of the interview to the participants. The interviews lasted on average around 50 minutes. The interviews were audio recorded with participants' permission. The results of the interviews were analysed with the use of the SPSS Statistics 21.0 software. The script of the interviews is presented in Appendix 1.

RESULTS

Company and Participants Characteristics

The interviews revealed that the majority of the companies commission their own employees as well as external consultants for the early assessment (reported 19 times). 15 participants reported that an early assessment is being performed only by people employed by the company, while only three stated that early assessment activities are fully performed by an external

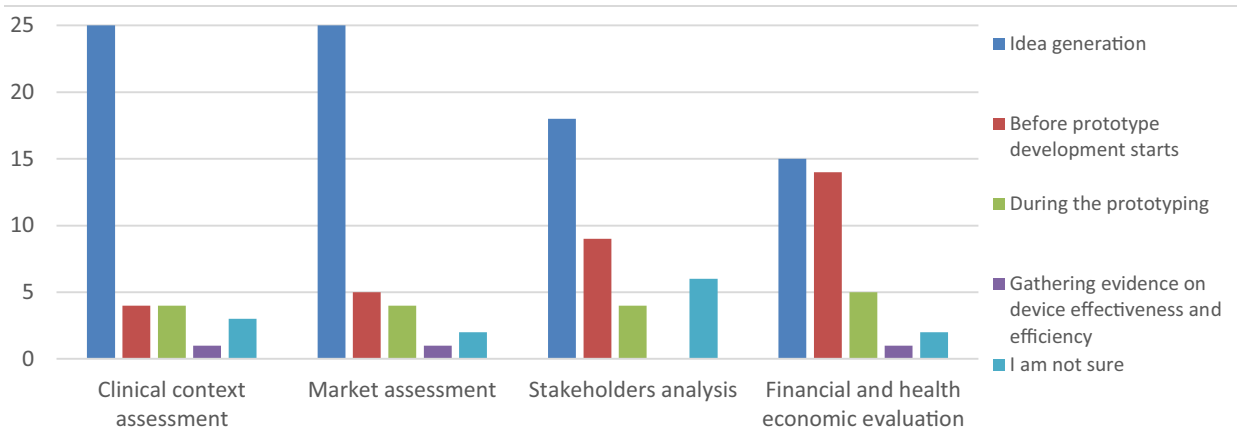


Figure 2a: An overview of the starting time of an assessment activities within four areas of an early assessment as indicated by the interviews participants.

consultant. Interviews revealed that the main reason for the companies to search for an external help for the early assessment of medical devices is the lack of an expertise within the company (N=18). Some participants stated that hiring external assessors is more efficient, e.g. cheaper (six participants), or more time-efficient (mentioned twice). Internal assessments are mostly performed by an individual employees assigned to particular tasks (N=22), or performed within the specialized departments within the company, e.g. R&D and Sales and Marketing department (N=14). Six participants stated that an early assessment in their companies is performed by assigning particular tasks to multiple people. Finally, two participants admitted that they are not sure how an early assessment was organised within their company. The characteristics of the interviews participants is presented in table A1 in Appendix 2. The characteristics of the companies participating in the interviews is presented in table A2 in Appendix 2.

An Early Assessment Methods used within the Companies

An overall assessment activities conduction

When asked to indicate the start of the assessment activities based on six roughly defined medical device development stages, it seemed that clinical context and market assessment have the highest priority, as both start at idea generation for the majority of companies. A smaller number of companies also start stakeholder analysis (n=18) and financial and health economic evaluation at the idea generation, while more companies postpone this to later stages. Figure 2a presents an overview of the stages where an assessment within four areas of an early assessment started as reported within the Dutch medical devices industry.

When asked to indicate when the assessment activities stop, the majority of the participants (reported 30-31 times) indicated all the areas of an assessment activities last until the post-marketing surveillance. Figure 2b presents an overview of the ending time of an assessment activities within four areas of an early assessment as indicated by the interviews participants.

Clinical context assessment

To analyze the clinical impact and need several performance indicators were of interest to the medical device developers: (1) potential device efficacy/effectiveness (N=32), (2) potential target population size (N=30), (3) safety and tolerability of the device (N=24), (4) patient satisfaction with the device (N=23), and (5) the severity of the disease that medical device is targeted at (N=15).

In order to evaluate these indicators, companies use different information sources, e.g. talking with the patients and clinicians (key-opinion leaders, KOL) (N=22), attending (clinical) conferences, events/trade shows (N=21), and reading scientific journals (N=20) (see figure 3).

Market assessment

The market analysis as a part of an early assessment in this research was assumed to be based on the analysis of the future users and the comparison to other interventions used for the disease. The majority of the respondents reported that the user analysis is mainly based on literature reviews of user needs (N=32), safety and

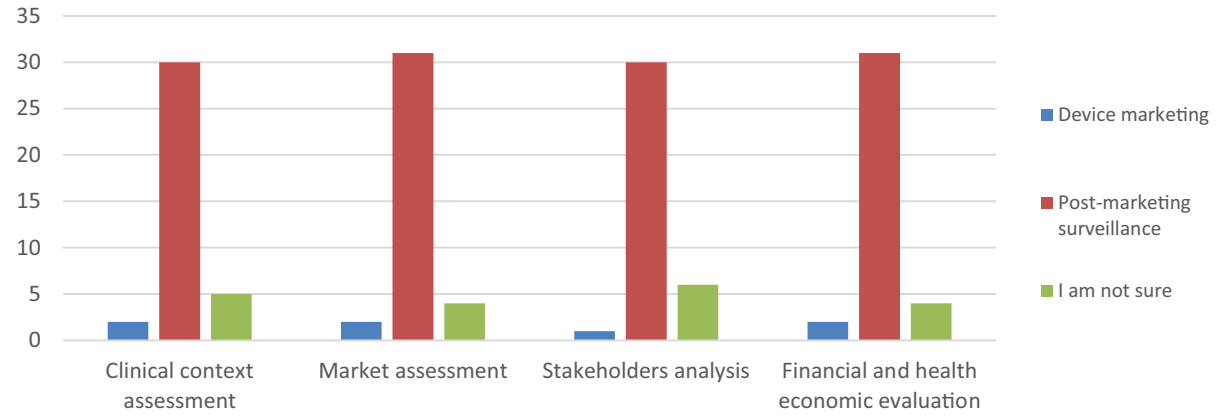


Figure 2b: An overview of the ending time of an assessment activities within four areas of an early assessment as indicated by the interviews participants.

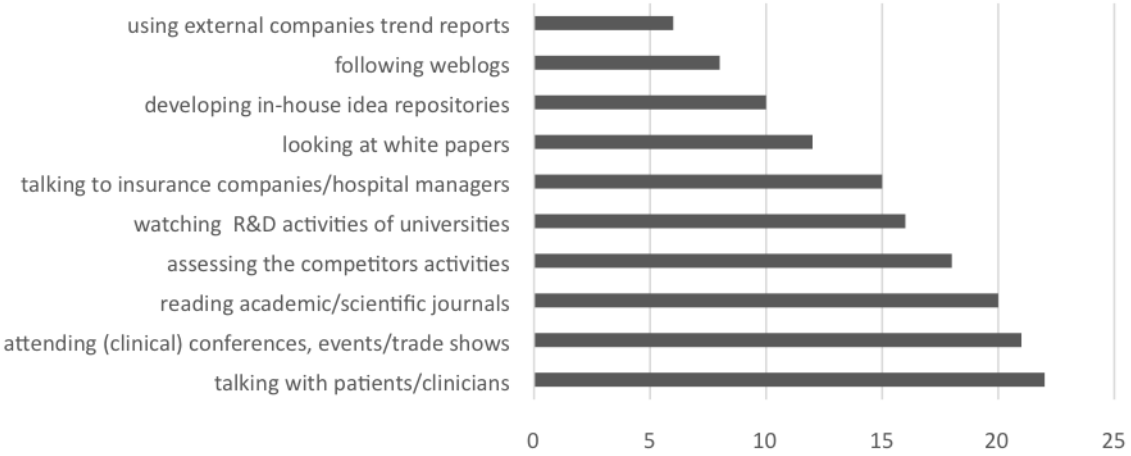


Figure 3: An overview of the information sources used to assess the clinical impact criteria within the medical devices industry.

usability testing (N=31), and informal and/or accidental meetings with users (N=29) (see figure 4a). The analysis of the alternative medical devices and interventions is mainly based on experts (KOL) consultation (N=30), monitoring industrial news sources (N=27), and patent searches (n=26) (see Figure 4b).

Stakeholders analysis

The analysis of the stakeholders within the medical device industry is based on the views of the experts and key decision makers within the medical device field of application. The participants reported that two dominating methods were present to gather those opinions, i.e. informal discussions (N=22), and formal consultation (n=21) (figure 5).

Financial and health economic evaluation

With respect to the financial analysis, most participants reported that in their company an extensive financial analysis from the company perspective is conducted (N=34), followed by financial analysis from the buyer (health insurance or hospital) perspective (N=29). Finally, least interviewees reported a full health economic evaluation, i.e. an evaluation of the incremental societal benefits against the incremental costs to society (N=22).

The financial analysis from the company perspective is usually supported by three methods, i.e. price determination (N=31), net present value using discounted cash flow analysis (N=30), and return on investment analysis (N=29) (figure 6). The financial analysis from the buyer perspective is supported with the Budget Impact Analysis (N=29), and with the return on investment

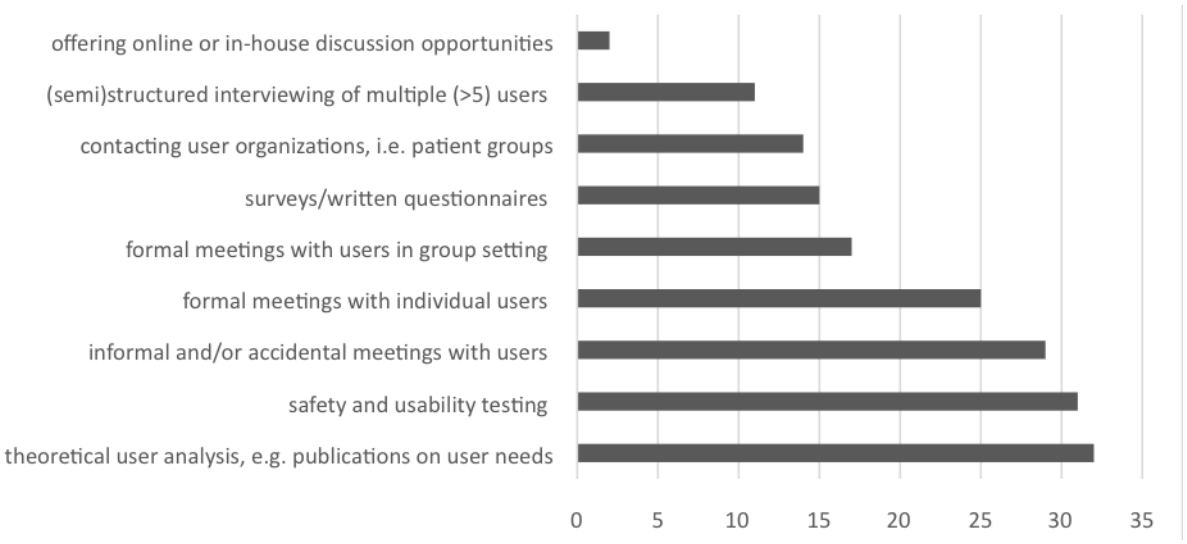


Figure 4a: An overview of the methods used to assess the future users perspective of medical devices under development.

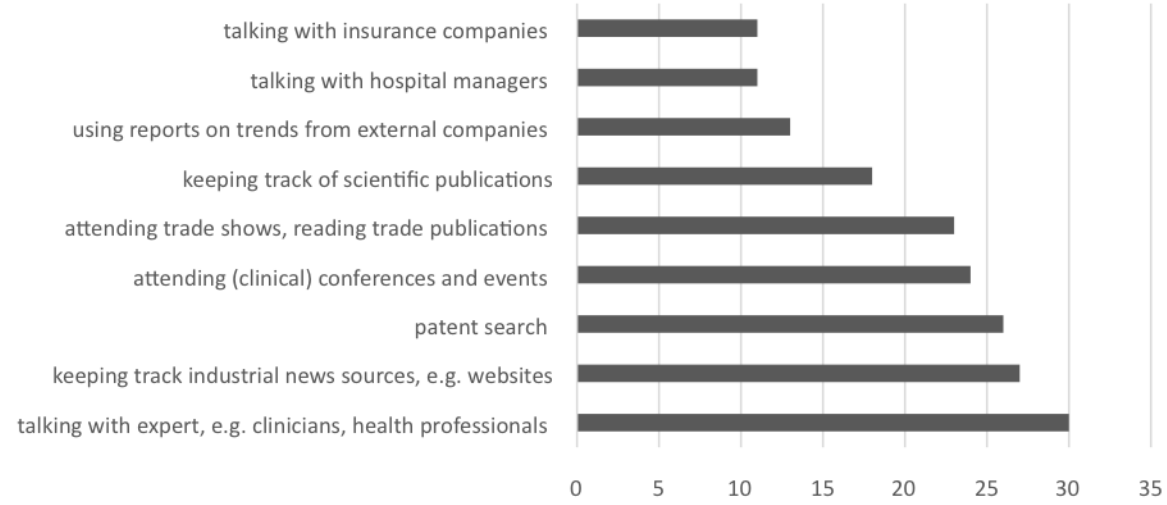


Figure 4b: An overview of the methods used to assess potential competitors of medical devices under development.

(N=21). Interviewees reporting on a health economic evaluation did mention cost-benefit analysis (N=18), cost-effectiveness analysis (N=16), and use the least – cost-utility analysis (N=7).

DISCUSSION

With the increasing regulatory demands for medical device SMEs and the need for efficient allocation of resources, a thorough understanding of the regulatory environment and its mechanisms to build the evidence at early stages of product development is required. This study interviewed key-personnel from medical device companies involved in R&D and market access and concluded that most companies do several assessments along the product development pipeline. Most of the assessment activities start early in the development of the medical devices (at the idea generation stage) and are conducted iteratively up to the post-marketing surveillance stage.

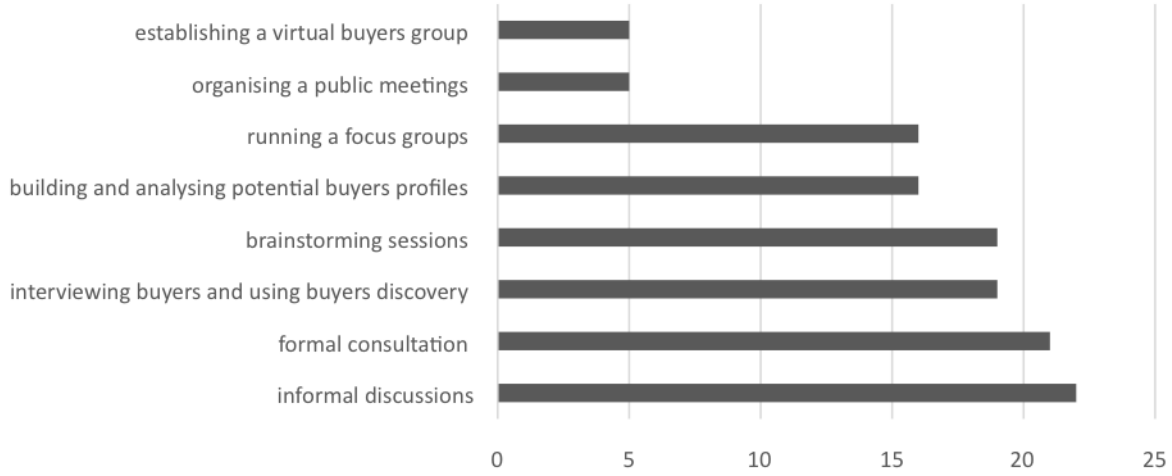


Figure 5: An overview of the methods used to gather the opinions of experts and decision-makers.

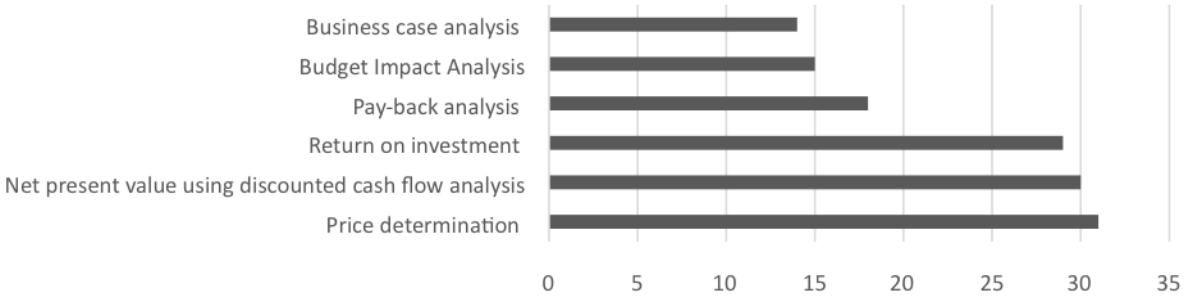


Figure 6: An overview of the methods used to perform an economic evaluation from the company perspective.

Although this research was not solely focused on SMEs, more than half of the companies participating in this study were SMEs (N=19), and 11 were a micro-sized spin-off companies with less than 10 employees. Almost half of the interviews participants, which were selected as the "key-informants" in the topic, reported a medium level knowledge (N=18) of the medical devices health technology assessment procedures, and one fourth indicated low/basic knowledge. This led to the conclusion that, although early assessments was considered important, most companies do not have in-house capacity and knowledge to perform health technology assessment. Previous research on the health economics activities within the English medical device industry performed by Craven et al.[14] seems to confirm the findings of this research with regard to the varying levels of health economics knowledge within the medical device industry. The main recommendation of Craven et al. was actually to increase the focus on the education needs, and tools to support the application of various health economics/assessment tools within the industry.

With regard to the different areas of the assessment activities as distinguished in this study, it is clear that the current focus is on the evaluation of the clinical context of the medical device and the assessment of the potential market. These assessments are mostly performed informally with interviews and stakeholder meetings. The majority of the companies use only the conversations with the clinicians and patients (N=22) and attending clinical conferences and trade shows (N=21) as an actual source to inform the clinical context. No formal quantitative methods presenting the opportunities for new products and the needs of patients are performed, while these could contribute to the validity and quality of the information that is collected.

The financial and business case evaluations within the medical device industry seems to be well developed with return on investment as a main driver and price setting as the objective. Although such analysis is essential for business planning and attractive venture capital, it does not reflect the perspective of the society in which the medical devices will operate. The societal perspective, i.e. the question whether society is willing to allocate

scarce resources to implement and/or reimburse the new medical device, is at best only marginally performed or understood from the companies perspective. This is disappointing, as the business case might be unreliable if the societal benefits are not considered. Markiewicz et al. proposed a simple method to illustrate how the expected societal benefits of the new product can be used for value-based pricing[23].

The results of this study confirm that medical device industry is very specific. It is characterized with very high level of innovativeness, strong technology push and a not very well developed market access and pricing strategy. It is build up mostly from SMEs managed by executives with strong scientific or technical background and oversimplified view of business and management issues[24]. That leads to the situation where other than technological advantages aspects, which significantly influence future implementation and adoption of medical device, e.g. the potential stakeholders requirements, are mostly overlooked[25]. At the same time the majority of the SMEs within the medical device industry focus on the development of a disruptive technologies, for which it is difficult to find the way to economically viable products[5]. A truly innovative medical device may offer the ability to significantly improve patients care, however proving safety, efficacy and regulatory compliance is often too challenging and costly for SMEs[26,27].

Inability of the SMEs to provide strong evidence of the potential societal value of their medical device under development makes it very difficult, or even impossible for most of them, to find investors willing to support their projects. As the healthcare resources are getting more and more stringent, the ability of a company to prove to potential investors that their technology will be cost-effective became a compelling argument supporting its future development[28]. The development of medical device from concept to product on the market can take up to a decades and significant investment is often needed before the medical device can even reach the first stage of clinical investigation[5]. In the same time the coverage and reimbursement by health insurance have a strong direct impact on the manufacturers attainable revenues[29]. Although there is a debate going on how assessment of an innovation early in the lifecycle could provide answers for insurers on the issue of funding the new technology and allow early patient access, the direct collaboration between medical device industry and insurance companies is still in the learning phase[7,30].

Although medical device manufacturers are operating in high technology multi-stakeholder environments they often fail to recognize the importance of the stakeholders analysis and they face the challenge of finding the right people to collaborate with[5]. For the medical device manufacturers it is therefore important to start an early dialogues with various stakeholders to understand the evidentiary requirements of various decision-makers involved in the implementation process. That could also help to better align perspectives on the potential value that the medical device could introduce to the healthcare system[31].

CONCLUSION

Although many methods seem to be in use within the medical device industry, there is no clear understanding of how those methods are conducted, what evidential requirements are to be met and how this supports the decision-making process in companies. To improve the assessment of the medical devices, a structured guidance of best practices would greatly benefit the industry as a whole.

ACKNOWLEDGMENT

This research was committed under a grant assigned by Province Overijssel and EU for NIRION Project within GO EFRO 2007–2013, and within High Tech Health Farm Program granted by Overijsselse Centra voor Research & Innovatie.

REFERENCES

1. Linehan, J.H. et al (2007) Medical Device Development Models - Final report. Stanford University Press. In Health – The Institute for Health Technology Studies.
2. Eng, T.R. (2004) Population health technologies: Emerging innovations for the health of the public. *American Journal of Preventive Medicine* 26(3): 237–242.
3. Chatterji, A.K. (2009) Spawned with a silver spoon? Entrepreneurial performance and innovation in the medical device industry. *Strategic Management Journal* 30(2): 185–206.
4. Imelli, P., Kobe, C. and Székely, G. (2006) Long term forecast of medical device markets through integration of scenario technique and Delphi method. Proceedings of the 5th International Conference on the Management of Healthcare and Medical Technology (HCTM). ETH-Zürich.
5. Davey, S.M., Brennan, M., Meenan, B.J. and McAdam, R. (2011) Innovation in the medical device sector: an open business model approach for high-tech small firms. *Technology Analysis & Strategic Management* 23(8): 807–824.

6. Kaplan, A.V., Baim, D.S., Smith, J.J., Feigal, D.A., Simons, M., Jefferys, D., Fogarty, T.J., Kuntz, R.E. and Leon, M.B. (2004) Medical Device Development from Prototype to Regulatory Approval. *Circulation* 109(25): 3068–3072.
7. Siebert, M., Clauss, L.C., Carlisle, M., Casteels, B., de Jong, P., Kreuzer, M. et al. (2002) Health technology assessment for medical devices in Europe. *International Journal of Technology Assessment in Health Care* 18(3): 733–740.
8. Vallejo-Torres, L., Steuten, L. M., Buxton, M. J., Girling, A. J., Lilford, R. J. and Young, T. (2008) Integrating health economics modeling in the product development cycle of medical devices: a Bayesian approach. *International Journal of Technology Assessment in Health Care* 24(4): 459–464.
9. The Council of the European Communities (1993) Council Directive 93/42/EEC.
10. Banta, D. (2003) The development of health technology assessment. *Health Policy* 63(2): 121–132.
11. Douma, K.F.L., Karsenberg, K., Hummel, M.J.M., Bueno-de-Mesquita, J.M. and Van Harten, W.H. (2007) Methodology of constructive technology assessment in health care. *International Journal of Technology Assessment in Health Care* 23(2): 162–168.
12. Royal Netherlands Academy of Arts and Sciences, KNAW (2014) Evaluation of new technology in health care - In need of guidance for relevant evidence. KNAW. Amsterdam.
13. EU Law and Regulations (2016) Proposal for a Regulation of the European Parliament and of the Council on medical devices, and amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009. European Union.
14. Craven, M.P., Allsop, M.J., Morgan, S.P. and Martin, J.L. (2012) Engaging with economic evaluation methods: insights from small and medium enterprises in the UK medical devices industry after training workshops. *Health Research Policy and Systems* 10(1): 29–37.
15. Markiewicz, K., van Til, J.A. and IJzerman, M.J. (2014) Medical devices early assessment methods: systematic literature review. *International Journal of Technology Assessment in Health Care* 30(2): 137–146.
16. IJzerman, M.J. and Steuten, L.M.G. (2011) Early assessment of medical technologies to inform product development and market access: A review of methods and applications. *Applied Health Economics and Health Policy* 9(5): 331–347.
17. Pietzsch, J.B. and Paté-Cornell, M.E. (2008) Early technology assessment of new medical devices. *International Journal of Technology Assessment in Health Care* 24(1): 36–44.
18. Vallejo-Torres, L., Steuten, L., Parkinson, B., Girling, A.J. and Buxton, M.J. (2011) Integrating Health Economics into the Product Development Cycle. *Medical Decision Making* 31(4): 596–610.
19. Schensul, S.L., Schensul, J.J. and LeCompte, M. (1999) Essential ethnographic methods. Walnut Creek. CA: AltaMira Press.
20. Hilgerink, M.P., Hummel, J.M. Manohar, S. Vaartjes, S.R. and IJzerman, M.J. (2011) Assessment of the added value of the Twente Photoacoustic Mammoscope in breast cancer diagnosis. *Medical Devices: Evidence and Research* 2011(4): 107–115.
21. Fermont, J.M., Douw, K.H.P., Vondeling, H. and IJzerman, M.J. (2016) Ranking medical innovations according to perceived health benefit. *Health Policy and Technology* 5(2): 156–165.
22. Thokala, P., Devlin, N., Marsh, K., Baltussen, R., Boysen, M., Kalo, Z., Longrenn, T., Mussen, F., Peacock, S. and Watkins, J. (2016) Multiple Criteria Decision Analysis for Health Care Decision Making—An Introduction: Report 1 of the ISPOR MCDA Emerging Good Practices Task Force. *Value in health* 19(1): 1–13.
23. Markiewicz, K., van Til, J.A., Steuten, L.M.G. and IJzerman, M.J. (2016) Commercial viability of medical devices using Headroom and return on investment calculation. *Technological forecasting and social change* 112: 338–346.
24. Brown, A. and Soderstrom, E. (2002) Start-up and equity primer. Yale: Association of University Technology Managers Publication.
25. Martin, J.L., Norris, B.J., Murphy, E. and Crowe, J.A. (2008) Medical device development: The challenge for ergonomics. *Applied Ergonomics* 39(3): 271–283.
26. Chesbrough, H.W. (2003) Open innovation: The new imperative for creating and profiting from technology. Harvard Business Press.
27. Chesbrough, H.W. and Garman, A.R. (2009) How open innovation can help you cope in lean times. *Harvard Business Review* 87(12): 68–76.
28. Cosh, E., Girling, A., Lilford, R., McAteer, H. and Young, T. (2007) Investing in new medical technologies: A decision framework. *Journal of Commercial Biotechnology* 13(4): 263–271.
29. Hartz, S. and John, J. (2008) Contribution of economic evaluation to decision making in early phases of product development: A methodological and empirical review. *International Journal of Technology Assessment in Health Care* 24(4): 465–472.
30. Levin, L. (2015) Early evaluation of new health technologies: The case for premarket studies that

harmonize regulatory and coverage perspectives. *International Journal of Technology Assessment in Health Care* 31(4): 207–209.

31. The Engelberg Center for Health Care Reform at Brookings. (2014) Biomedical innovation - Identifying challenges and prioritizing needs in medical device research and development. Discussion guide.

APPENDICES

Appendix 1. Interviews with MD companies executives.

I COMPANY BACKGROUND

1. What is your knowledge level on assessment of medical devices?

- good/expert;
- unmedium;
- low/basic.

2. Who performs assessment of medical devices in/for the company you work for?

- there are people in the company responsible for assessment performance;
- we hire external companies/people to assess devices;*
- we have both people in and outside the company assessing devices;*
- other:

3. *Why does your company hire external company/people to perform the assessment?

- there are no people capable of assessment performance in my company (lack of expertise);
- there are no people assigned to perform assessment in my company (lack of tasks specification);
- there in no time available to perform assessment in my company;
- hiring external company is more efficient (e.g. cheaper);
- other:

4. How does your company performs the tasks required for assessment of medical devices?

- individual people assigned to particular tasks;
- company department specialized in assessment performance;
- ad hoc decisions on who is responsible for particular tasks;
- particular tasks divided over multiple people.

5. How many people does the company employ at the moment?

6. Which country does the company mainly operate in?

7. What is the number of medical devices your company now works on/offers?

- On the market
- In the development
- Unsuccessful projects rate

8. What type of devices in the risk-based classification does your company mainly produce?

- Class I: simple, low risk devices
- Class II: more complex, higher risk
- Class III: most complex, highest risk

II MARKET ANALYSIS

9. What does your company look at when performing market analysis?

- clinical context of use (need analysis); (choose methods from ***LIST 1)***
- competitors (other companies operating in the area); (***LIST 2)***
- future users (doctors, patients, hospital managers). ***(LIST 3)***

List 1: CLINICAL CONTEXT OF USE

What sources does your company uses in the analysis of the clinical context of device use?

- reading academic/scientific journals;
- watching the activities of universities with departments engaged in medical devices R&D;
- attending (clinical) conferences and events/trade shows, reading trade publications;
- talking with patients/clinicians;
- developing in-house suggestion schemes/ idea repositories (e.g. intranet discussion boards);
- following weblogs;
- talking to insurance companies/hospital managers;
- assessing the competitors activities;
- using external companies trend reports;
- looking at white papers.

List 2: COMPETITORS

How do you (or your company) keep track of the competition during medical device development?

- keeping track of websites/blogs/other internet resources;

- talking with clinical experts/clinicians/ health professionals;
- attending trade shows, reading trade publications;
- talking with insurance companies and hospital managers;
- using reports on trends from external companies;
- attending (clinical) conferences and events;
- keeping track of scientific publications in research journals.

List 3: FUTURE USERS
How does your company involve the future user perspective in medical device development?

- user analysis (i.e. analysis of published materials on user requirements, user needs);
- safety and usability testing;
- informal and/or accidental meetings with users;
- seeking contact with user organizations (i.e. patient groups);
- formal meetings with individual users;
- formal meetings with users in group setting;
- (semi)structured interviewing of multiple (>5) users;
- by offering online or in-house discussion opportunities;
- surveys/written questionnaires.

10. How do you or does your company estimate the potential of the medical device in the clinical context?

- the clinical impact (increase in effectiveness of care) of the new device; (***LIST 4)***
- costs of new device (for the company, for potential buyers, social costs); (***LIST 5)***
- opinions of experts and decision makers; (***LIST 6)***

List 4: CLINICAL IMPACT
What does your company include in the clinical impact analysis of a medical device?

- disease severity (e.g. life threatening);
- the size of the target population;
- the improvement of efficacy/effectiveness (of cure or care);
- the improvement of safety & tolerability (of cure or care);
- the improvement in patient satisfaction.

List 5: ECONOMIC EVALUATION
What methods does your company use to estimate costs from the company perspective?

- estimation of the future selling price of the device based on manufacturing cost, market place, competition, market condition, and device quality;
- estimation of the profitability of the project based on potential costs and revenues;
- estimation of the return on investment on medical device;
- estimation of how long it will take before the investment in the medical device will be recouped;
- comparison of different business cases for one device, or for different devices to select the device with the highest potential for the company;
- estimation of the profitability of the project based on potential costs and revenues while including the probability of achieving the revenues.

What methods does your company use to estimate costs from the buyer perspective?

- estimation of the financial impact of new device in its future setting (i.e. hospital, etc.);
- estimation of the future return on investment on new medical device for the buyer.

What methods does your company use to estimate costs from the societal perspective?

- cost-effectiveness analysis;
- cost-utility analysis;
- cost-benefit analysis.

List 6: EXPERTS/DECISION MAKERS
How does your company gather opinions of the experts and decision makers?

- building and analyzing potential buyers profiles;
- running a focus groups;
- organizing a public meetings;

- interviewing buyers and using buyers discovery;
- formal consultation;
- brainstorming sessions;
- informal discussions.

11. When does market analysis start?

- idea generation;
- before the development of the device prototype starts;
- during the device prototyping;
- when gathering evidence on effectiveness and efficiency of the device;
- during marketing of the device;
- I don't know.

12. When does market analysis stop?

- idea generation;
- before the development of the device prototype starts;
- during the device prototyping;
- when gathering evidence on effectiveness and efficiency of the device;
- during marketing of the device;
- I don't know.

13. How is, in your opinion, market analysis usually performed?

- one off exercise;
- iterative/repetitive process.

14. Has the market analysis of the medical device ever led its further development to be:

- accelerated;
- stopped;
- decelerated;
- altered;
- none of these;
- I don't know.

III ECONOMIC EVALUATION

15. From which perspective(s) does your company estimate the costs aspects of the medical device?

- company perspective (e.g. production costs, profit margins, production capacity);
- buyer perspective (e.g. impact on hospital budget, spending and savings incurred by implementing the product in the setting);
- societal perspective (e.g. long term costs consequences on societal spending on health care and revenues with regard to working life years gained).

16. Has the analysis of the cost impact of a medical device from the company/buyer/societal perspective ever led its further development to be:

Company perspective:	Buyer perspective:	Societal perspective:
- accelerated;	- accelerated;	- accelerated;
- stopped;	- stopped;	- stopped;
- decelerated;	- decelerated;	- decelerated;
- altered;	- altered;	- altered;
- none of these;	- none of these;	- none of these;
- I don't know.	- I don't know.	- I don't know.

17. When does your company start with the analysis of a medical device costs?

- idea generation;
- before the development of the device prototype starts;
- during the device prototyping;
- when gathering evidence on effectiveness and efficiency of the device;
- during marketing of the device;
- I don't know.

18. When does analysis of medical device costs stop?

- idea generation;
- before the development of the device prototype starts;
- during the device prototyping;
- when gathering evidence on effectiveness and efficiency of the device;
- during marketing of the device;
- I don't know.

19. How is, in your opinion, analysis of costs of a medical device usually performed in your company?

- one off exercise;
- iterative/repetitive process.

IV EXPERTS/DECISION MAKERS ANALYSIS

20. Who do you or your company consider experts or decision makers in medical device development process?

21. When are the opinions of experts/decision makers on medical device first gathered?

- idea generation;
- before the development of the device prototype starts;

- during the device prototyping;
- when gathering evidence on effectiveness and efficiency of the device;
- during marketing of the device;
- I don't know.

22. When the gathering of opinions of experts/decision makers on medical device stops?

- idea generation;
- before the development of the device prototype starts;
- during the device prototyping;
- when gathering evidence on effectiveness and efficiency of the device;
- during marketing of the device;
- I don't know.

23. Has the consultation of experts/decision makers ever led its further development to be:

- accelerated;
- stopped;
- decelerated;
- altered;
- none of these;
- I don't know.

V RESPONDENT BACKGROUND

24. What is your age in years?
25. What is your education level?
26. What is your education background (Business management, Economist, etc.)?
27. What is your position in the company?
28. Which department within company do you work in?
29. How many years of experience (in that position) do you have?

VI USE OF MEDICAL DEVICE ASSESSMENT

What, in your opinion, are the uses of performing assessment for medical devices under development?

- increase understanding of design, usability and safety of a medical device;
- aid decision making with regard to design, usability and safety of a medical device;
- increase understanding of device impact (e.g. potential clinical and economic value);
- aid decision making with regard to device impact (e.g. uptake in the market).

Appendix 2. Table A1 presents an overview of the companies that participated in the study. Table A2 presents an overview of the participants of the interviews.

Table A1: An overview of the companies that participated in the study (N=36)

Characteristics	Description	N
Company size	micro-sized company (less than 10 employees)	11
	small-sized company (10-50 employees)	15
	medium-sized company (50-250 employees)	4
	large-sized company (more than 250 employees)	6
Operating country	the Netherlands	27
	International	9
Risk classes of devices produced	Class I: simple, low risk devices	25
	Class II: more complex, higher risk	29
	Class III: most complex, highest risk	13
	only one device class	18
	more than one device class	19
Devices in development	0	2
	1-3	13
	4-6	5
	6-10	4
	>10	2
Devices on the market	0	8
	1-3	7
	4-6	6
	6-10	2
	>10	4

Table A2: An overview of the participants of the interviews.

Characteristics	Description	N
Position in the company	CEO	10
	Manager	14
	Business developer	5
	Researcher	4
	Engineer	4
Department in the company	No specific department	14
	R&D	16
	Sales & marketing	5
	Clinical department	2
Education level	Master degree	19
	PhD degree	13
	Bachelor degree	4
	Vocation education	1
Education background	Industrial design	6
	Economics	7
	Biomedical engineering	7
	Health sciences	4
	Other (e.g. Medicine, Engineering)	13
Respondents age	21-40	17
	41-60	16
	more than 60	4
Experience years	< 1	4
	1-5	11
	6-15	14
	>15	8
Assessment knowledge	good/ expert	10
	medium	18
	low/ basic	9

Article

Risk Assessment and Management in Hospital Merger and Acquisition

Li Han
Weifang People's Hospital, Weifang City, Shandong Province, China

Fei Ren
Weifang People's Hospital, Weifang City, Shandong Province, China

ABSTRACT

In recent years, the Chinese government has introduced a series of policies to promote the health care reform and further promote the hospital industry towards marketization, which makes the hospital M & A continue to heat up. In order to effectively integrate the existing resources, expand the operation scale, strengthen the comprehensive strength, improve the hospital's core competitiveness, make the M & A behavior more scientific to promote the deepening of the medical system reform, this paper studies the risk evaluation and management of M & A based on the theory of hospital M & A. The risks in the current M & A include financial risk, strategic risk, transaction risk, integration risk, etc. These risks will restrict the future development of hospitals, and even lead to the failure of mergers and acquisitions and huge economic losses. Therefore, correct risk assessment and management is the key to the success of M & A. By applying the qualitative identification method, the quantitative analysis method and the expert investigation method as well as making corresponding management adjustment and countermeasures, the risk probability can be reduced and the success rate of M & A can be improved so as to realize the strategic goal. In the hospital M & A, the use of risk assessment and management can prevent and evade risks, which enables the industry chain to extend, helps the development of the industry and provides better medical and health services for the people.

Journal of Commercial Biotechnology (2017) 23(2), 31–36. doi: 10.5912/jcb782
Keywords: hospital M&A, risk assessment, risk management

INTRODUCTION

With the accelerated process of economic integration, the world is facing with the tide of mergers and acquisitions and the means, type and scope of mergers and acquisitions are also increasing, which makes it one of the paths for the rapid development of many industries. With the introduction of policies related to investment in the medical industry, hospital mergers and acquisitions have become an important way for hospitals to achieve expansion. The economic essence of hospital M & A is no different from enterprise M & A, both of which are the common forms of capital operation under market economy conditions. Through mergers and acquisitions, the hospital accesses to advanced medical technologies, management experience, professionals and other resources to expand the scale of operation and forms an effective scale, thereby enhancing its core competitiveness. Mas N et al [1] discussed the role of technology in the selection of targets in a merger through the US case of hospital mergers and acquisitions. Ling Bing [2] analyzed the current status of hospital mergers and acquisitions, and thought that value assessment was a key issue in M & A. Kjekshus et al. [3] proposed that mergers were often complex and difficult processes with variable outcomes and hospitals were merging to become more cost-effective. However, hospital mergers and acquisitions bring many benefits but also a lot of risks, such as financial risk [4], strategic risk [5] and integration risk [6]. Therefore, it is necessary to grasp the risk evaluation and management in hospital M & A since good risk assessment and management can effectively avoid the risks in hospital merger and acquisition, and thus achieve a win-win situation of the merging party and the merged party.

Correspondence:
Fei Ren, Weifang People's Hospital, China. Email: renfei1122@sohu.com

Theoretical Significance of Hospital Mergers and Acquisitions

Hospital M & A [7], a way for hospitals to achieve expansion, takes hospital property rights as the transaction object, aims to obtain the right of control of the merged hospital and is realized by purchasing all or part of the property or assets of the acquired hospital in cash, securities or other forms. Successful hospital M & A not only helps to integrate resources, improve economies of scale, establish its dominant position in the medical industry, but also helps hospitals digest excess capacity, reduce operating costs and capital costs and enhance their value. The combined hospital can produce synergistic effect, resulting in the "1 +1> 2" effect. The advantages of both parties are complementary in talent, technology and finance aspects, which helps to improve the efficiency and level in management. For the time being, chain type specialized hospitals with good profits, strong replicability and small medical risks and level 2 and 3 general hospitals with certain scale and stable cash flow that can improve their performance through investment are most popular among investors and have become the mainstream of hospital mergers and acquisitions. Hospital M & A has important strategic significance, which not only can undertake excellent medical service projects and management systems as well as the customer resources accumulated over the years, but also can lay the foundation for the future development of hospitals, enhance their core competitiveness and build the benchmark of regional medical services.

RISK ASSESSMENT IN HOSPITAL M & A

There are a lot of risks in hospital merger and acquisition, among which the financial risk is the most prominent. Therefore, the management department should make risk assessment and timely management adjustments.

Financial Risks

As shown in Figure 1, hospital M & A includes strategic risk, transaction risk and integration risk. Financial risk runs through the whole process of M & A, and different stages of M & A have different financial risks.

Financial risk is a risk which can result in the decrease of the prospective profits of investors due to the loss of debt paying ability of the company resulting from unreasonable financial structure and improper financing. The financial risks in hospital M & A are mainly divided into the following three categories: In the decision-making stage, the acquirer blindly strives for the biggest profits and demands perfection, rushes for quick results while lacking the technology, management and market experience of the medical industry and makes wrong pricing decisions, leading to an incorrect value

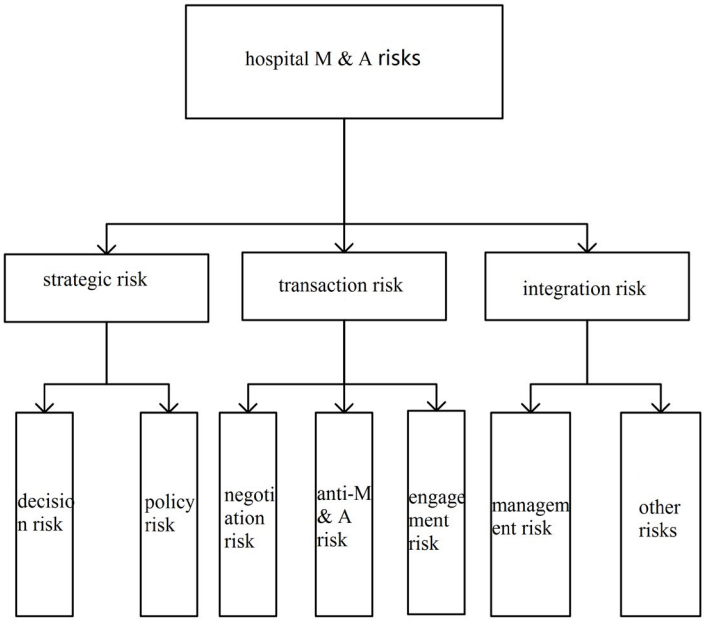


Figure 1: Hierarchy structure of hospital M & A risk

assessment; improper financing and the use of a single payment method in mergers and acquisitions can have a negative impact on capital structure and financial leverage; after mergers and acquisitions, resource integration decision-making errors can cause financial integration risks.

In this paper, the acquisition of an enterprise hospital (B) by a company (A) is taken as an example. In the early stage of M & A, if B does not provide accurate information to A, A and B have asymmetric information, and A's internal management personnel has low risk awareness, then, A can not make correct evaluation of B, which will lead to pricing risk. During M & A, if A's financing structure is unreasonable, its asset-liability rate is too high, its working capital turnover rate is insufficient, and its follow-up profitability is not enough to deal with the operation and repayment, there will be financial risk. After M & A, in this case, the information systems of A and B will be incompatible, the management cultures of both parties are in conflict with each other and their resources can not be efficiently integrated, triggering financial crisis, affecting the performance of both sides. These are derived from internal financial risks. The external financial risk mainly comes from the complexity of the financial management macro environment [8], including the economic environment, the legal environment, the market environment, the social cultural environment and the resource environment. The lack of attention to the macroeconomic environment and the forecast on its changes will result in the collapse of mergers and acquisitions.

Risk Assessment

Risk assessment [9] is a process to make an overall consideration, combining with other factors, of the probability of the occurrence of risks and the degree of loss and decide whether to take appropriate measures, on the basis of risk recognition. We take the acquisition of Haiyang People's Hospital of Shandong Province by the Affiliated Hospital of Qingdao University Medical College, Shandong Province (hereinafter referred to as the General Hospital) as an example. After the acquisition, Haiyang People's Hospital is known as Haiyang Branch of the Affiliated Hospital of Qingdao University Medical College (hereinafter referred to as Haiyang Branch). The qualitative identification method [10] and the quantitative analysis method [11] were used to determine the risk assessment benchmark and the overall risk level of the project. The individual risk was compared with the individual benchmark, the overall project level with the overall assessment baseline. When the project risk is still with an acceptable range, the project is still possible to continue. At the same time, expert survey method was used to evaluate the environmental risk of M & A by an expert evaluation team, marks were given by the experts according to the evaluation principle of Delphi method [12] and the final value was calculated by weighting with the same weight.

As shown in Fig. 2, the intrinsic value measurement risk is higher than the M & A environment risk in the M & A. The main risks are knowledge and innovation risk, valuation method risk and M & A market risk. In the acquisition process of Haiyang Branch, the value of the Haiyang Branch is relatively overpriced and there is pricing risk [13]. In order to avoid this risk, we need to further understand Haiyang Branch's financial status, liabilities, property rights structure, human resources

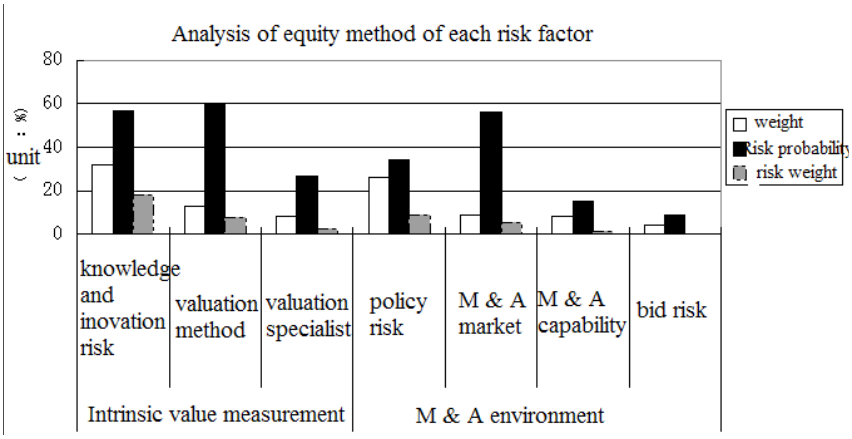


Figure 2: Analysis of the various risk factors equity method

and technical level, so as to ensure the objective authenticity of the information and strive for the positive cooperation of the Haiyang Branch as well as the support of the people's government. Before the acquisition, the medical environment and equipment configuration of Haiyang Branch is poor, the level of academic qualifications is not high, with irrational structure of titles and lagged management methods, but there are geographical and policy support for it. While the main advantages of the General Hospital are advanced scientific research level and management system, its main goal is to bring medical and health resources to rural grass-root areas. After the acquisition, the hospital's vertical service network extends to the rural areas to form a reasonable medical resources allocation pattern, to achieve scientific research guidance and personnel training to better solve the problem of difficulty of local people to see a doctor. Relying on the driving of technology, capital and brand of the general hospital, Haiyang Branch quickly improves the quality of service and medical level, introduces the advanced management mode of the general hospital and improves the original operating mechanism. The two sides quickly and efficiently complete the integration of resources to avoid the risk of financial integration and achieve a win-win situation.

As shown in Figure 3, after the merger, the personnel number of outpatient and emergency departments, the number of operations and the daily total number of occupied beds of the Haiyang Branch have improved significantly. It gradually develops into a comprehensive hospital integrating medical treatment, first aid, teaching, scientific research, prevention and health care. Reasonable risk assessment and corresponding adjustment in hospital M & A can greatly reduce the risk probability and achieve a win-win situation of both parties.

HOSPITAL M & A RISK MANAGEMENT

Risk management [14] is a management process that minimizes the adverse effects which can be probably caused by risks. During the M & A process, the hospital management department needs to take positive measures to prevent and control risks, to reduce the probability of loss. Effective risk management will help the hospital make the right decisions, protect the safety and integrity of assets and achieve the desired objectives. Facing with the financial risk in the M & A process, the Affiliated Hospital of Qingdao University Medical College in Shandong Province has taken corresponding risk management measures, making the acquisition to proceed smoothly, but there are still some shortcomings.

Status of Risk Management

Before the M & A decision, the general hospital objectively examined its own resource strength and reduced the blindness and subjectivity of the M & A strategy. However, in the preparatory stage, it was not fully aware of the importance of understanding each other's information and was lack of attention to the macro-market. Government attitudes towards M & A and changes in the external market environment will have a certain impact on M & A behavior. It is important for the acquirer to fully understand and carefully select the acquired hospital, in particular, its property rights, financial status, in order to make a scientific assessment of its value and reduce the probability of the occurrence of risks. Hospital M & A is related to government administrative

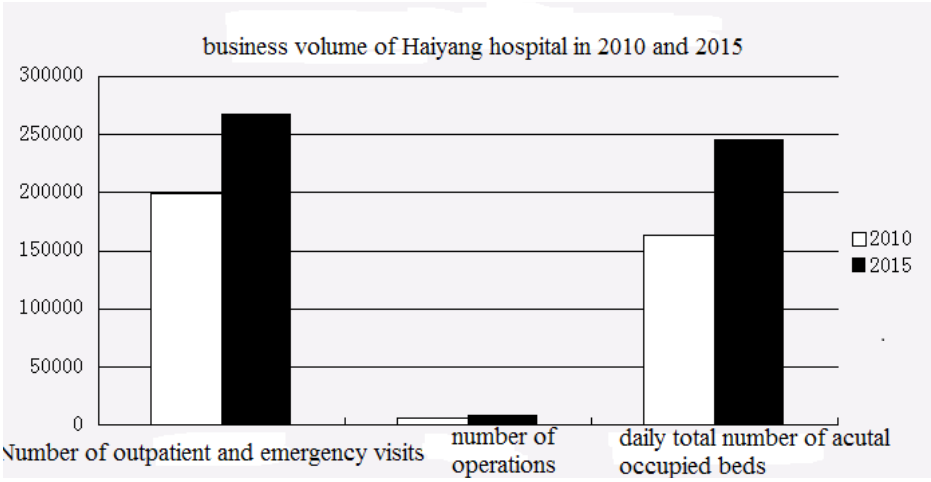


Figure 3: Business volume of Haiyang Branch in 2010 and 2015

intervention, financial, legal and other related policies, and each local policy is different from each other. Failure to get familiar with the local policy background of the acquired hospital will greatly affect the results of mergers and acquisitions. After the acquisition was completed, the general hospital carried out technical and financial resources integration in a timely manner, established a management mode focusing on the link management, strengthened the secondary management of the hospital, realized the complementary advantages of the medical institutions, shared the resources, optimized the layout and structure of the hospital, so as to maximize the resource efficiency, and promote long-term development of the hospital to enhance the core competitiveness of the hospital after the merger. However, there was a lack of integration in the hospital culture as well as attention of personnel placement after the acquisition.

Risk Management Recommendations

Set up a professional team, grasp the best time. Hospital M & A is not a simple capital operation, but a kind of merger and acquisition behavior affected by policies and the market. Hence, the establishment of a professional M & A team [15] is necessary. An M & A team composed of experts in finance and investment, management, law and other fields can solve the problems of more professionalism in M & A process, make the hospital merger more scientific, improve the efficiency of hospital reorganization and asset management, and form a supervision mechanism to avoid risks. Meanwhile, the timing of the merger is equally important.

Emphasis on cultural integration and good placement work. The completion of M & A is not the end, but the beginning of formal management. Employees are the fundamental part of the enterprise and the employee placement work after acquisition must be actively arranged. The personnel appraisal system and reward and punishment mechanism should be improved, with dynamic supervision, to fully mobilize the enthusiasm of the staff. Regular organization of professional and technical personnel to learn advanced management knowledge should be carried out in order to strengthen the quality education of the staff. Since hospital culture is the essence of the hospital, attention should be paid to the organic integration of the hospital culture after the merger, and the enhancement of the cultural construction and cohesion as well as the staff's mental outlook.

DISCUSSION AND CONCLUSION

With the intensification of competition in the medical market in China, hospital mergers and acquisitions have gradually become the social capital and entered into the hospital industry. Nevertheless, opportunities and challenges coexist. On the one hand, successful mergers and acquisitions will help the two sides to achieve complementary advantages and the sharing of resources, which enables the industrial chain to expand, makes health care services more comprehensive and enhances the hospital's core competitiveness; on the other hand, it has many pitfalls, such as financial risk, strategic risk and integration risk, which may hinder the M & A and may even bring huge economic losses. This requires good risk assessment and management work in hospital M & A. Therefore, during the M & A process, multi-party information should be acquired, the value of the merged party should be scientifically assessed, a professional team should be formed, the best time should be grasped and the governance structure and management mechanism should be improved. After the M & A process, effective reorganization of assets and cooperative management should be carried out so as to complete technological, cultural and personnel integration.

By taking the acquisition of Haiyang People's Hospital of Shandong Province by the Affiliated Hospital of Qingdao University Medical College as an example, this paper carries out a risk assessment study and puts forward the corresponding management measures and improvement suggestions. However, practical measures of risk management in different stages still need to be further explored.

REFERENCES

1. Mas, N. and Valentini, G. (2015) Technology complexity and target selection: the case of US hospital mergers. *Industrial & Corporate Change* 24(2): 511–537.
2. Ling Bing. (2015) Hospital M & A and hospital valuation. *Operators* (7): 26–26.
3. Kjekshus, L.E., Bernstrøm, V.H. and Dahl, E. et al. (2014) The effect of hospital mergers on long-term sickness absence among hospital employees: a fixed effects multivariate regression analysis using panel data. *BMC Health Services Research* 14(1): 50.
4. Hou Xiaofeng. (2014) Financial risk analysis and control strategy in M & A. *Management Review* (1): 69–70.
5. Hegde, S.P. and Mishra, D.R. (2017) Strategic risk-taking and value creation: Evidence from the market for

corporate control. *Social Science Electronic Publishing* 48: 212–234.

6. Bo, E., Kleinaltenkamp, M. and Tronvoll, B. et al. (2014) Institutional logics matter when coordinating resource integration. *Marketing Theory* 14(3): 291–309.
7. Sun, X. and Zhu, S. (2016) A case study of hospital merger based on close medical consortium. *Finance and Accounting Research* (17): 219–220.
8. Dong Suorang. (2015) The micro-environment and macro-environment of financial management. *Consumer Guides* (8): 123–123.
9. Lee, J. and Prékopa, A. (2015) Decision-making from a risk assessment perspective for Corporate Mergers and Acquisitions. *Computational Management Science* 12(2): 243–266.
10. Abdolshah, M. (2015) Fuzzy quantitative and semi-qualitative risk assessment in projects. *International Journal of Risk & Contingency Management* 4(2): 20–30.
11. Peng, X.Q. and Lu, T.T. (2014) Evaluation and analysis of the quantitative computing model of the information security risk assessment. *Applied Mechanics & Materials* 543–547: 3565–3568.
12. Kauko, K. and Palmroos, P. (2014) The Delphi method in forecasting financial markets— An experimental study. *International Journal of Forecasting* 30(2): 313–327.
13. Peeperkorn, J. and Seetharam, Y.A. (2014) Proposed model to behaviourally pricing risk. *Journal of Economics & Behavioral Studies* 6(6): 477–487.
14. Garfinkel, J.A. and Hankins, K.W. (2010) The role of risk management in mergers and merger waves. *Ssrn Electronic Journal* 101(3): 515–532.
15. Wan, G. and Zhou, J. (2014) Top management team demographic faultlines, firm visibility and firm acquisition activity in China. *Academy of Management Annual Meeting Proceedings* 2014(1): 15342–15342.

Article

Statistical Optimization of the Production of α-Amylase From *Bacillus licheniformis* MTCC 1483 Using Paddy Straw as Substrate

Palki Sahib Kaur
Department of Biotechnology, CGC, Landran, Mohali, I.K.G.Punjab Technical University, Kapurthala, India

Sukhjeet Kaur
Department of Biotechnology, SUSCET, Tangori, India

Hardish Kaur
Department of Biotechnology, CGC, Landran, Mohali, I.K.G.Punjab Technical University, Kapurthala, India

Sonica Sondhi
Department of Biotechnology, Government College for Girls Sec. 42, Chandigarh, India

ABSTRACT

α-Amylase has been in increasing demand in industries due to its hydrolytic nature. Solid state fermentation (SSF) is a cost effective method for increasing the enzyme production. In the present study, amylase from *Bacillus licheniformis* MTCC 1483 was produced in large quantity by solid state fermentation using paddy straw as substrate. Response surface methodology is a useful tool for optimizing many parameters at a time and is used for increasing the amylase production. 8523 IUg-1 of enzyme activity was obtained under optimized conditions which lead to 35 fold increase in the yield of amylase from unoptimized condition.

Journal of Commercial Biotechnology (2017) 23(2), 37–45. doi: 10.5912/jcb784
Keywords: *Bacillus licheniformis*, Amylase, Solid state fermentation, Response surface methodology

INTRODUCTION

Paddy straw is one of the most abundant lignocellulosic wastes on the earth. In India, total annual production of rice was 136.5 million tons in the year 2009[1]. About 1-1.5 kg of straw is produced from every kilogram of the grain harvested[2] and thus, 136.5-150 million tons of paddy straw is estimated to be produced annually. In India, approximately 85-95 million tons of paddy straw is disposed off by burning. One ton of paddy straw burning releases 3 kg particulate matter, 60 kg CO, 1460 kg CO_2, 199 kg ash and 2 kg SO_2[3]. Lung and respiratory diseases caused by burning adversely affect public health[4]. Repeated burning of paddy straw also results in soil erosion. Moreover, farmers offer rice straw as the main roughage source to their animals. But, the high level of lignification and silicification, the slow and limited ruminal degradation of the carbohydrates and the low content of nitrogen are the main deficiencies of rice straw, affecting its value as feed for ruminants[5].

Paddy straw due to its high nutritional value can be employed as a source of enzyme production. Solid state fermentation is a useful method for the production of enzymes in high yield. SSF employs low cost substrate to produce large quantity of enzyme with relatively low cost[6]. Solid substrate fermentation (SSF) is cheaper, less technology oriented and the enzyme extraction is relatively easier than submerged fermentation as the release of liquid effluent is negligible and hence produces less pollution[7]. α-amylase (E.C. 3.2.1.1.) is a hydrolytic enzyme which

Correspondence:
Mrs. Palki Sahib Kaur, Chandigarh Group of Colleges, India. E-mail: palki.cct@gmail.com

cleaves α-1,4 glycoside linkages in starch, yielding dextrin, oligosaccharide, maltose and glucose[8,9]. It is one of the most extensively used enzymes in various industries like pharmaceutical, food, textile, paper, detergent and fuel ethanol production industry[8,10,11]. Various Agro industrial wastes have been utilized for the cost effective production of alpha amylase and researchers are finding great interest in using agro industrial waste as a substrate for alpha amylase production[12]. Previously, we had optimized the production of amylase from *Bacillus licheniformis* MTCC 1483 in SSF using paddy straw as substrate by employing traditional one variable at a time method (OVAT)[13].

Although, OVAT method is helpful in selecting parameters significantly affecting the enzyme production, the method is not only time restrictive, but also ignores the combined interaction(s) among various physical and nutritional parameters. On the other hand, the statistical methods such as Plackett-Burman (PB) and response surface methodology (RSM) are useful models for selecting significant factors and studying the interactive effect of these factors. These methods give mathematical models showing the dependence of the response (enzyme yield) on independent variables which are used for the prediction of optimum values of these variables, ensuring maximum yield. They also reduce the number of experiments required in optimization. Use of factorial designs and regression analysis for generating empirical models makes RSM a good statistical tool. Therefore, in this study, to analyze the collective effect of various factors, Plackett-Burman (PB) and response surface methodology (RSM) were used for the optimization of amylase production from *Bacillus licheniformis* MTCC 1483 using paddy straw as solid substrate and thereby reducing the burning of paddy straw as a methods used for paddy straw disposal.

MATERIALS AND METHODS

Chemicals

The chemicals used in the study were of analytical grade obtained from Hi-media (India). The solid substrate paddy straw was taken as a substrate for the production of α- amylase by SSF[13]. They were procured from local market of Mohali, Punjab, India. Substrate was washed with distilled water 2-3 times and then treated with 1% NaOH for 30 min and dried in oven at 80°C overnight. Dried substrates were ground in the grinder and sieved through a mesh to obtain equal size particles.

Microorganism and Growth Conditions

The bacterial strain used in this study, *Bacillus licheniformis* MTCC 1483 producing extracellular amylase was obtained from MTCC, Institute of Microbial Technology (IMTECH), Chandigarh, India. The bacterial strain was revived in Brain heart infusion broth. The bacterial strain was sub-cultured periodically after 4 days and stored at 4°C until further use.

Amylase Assay

Amylase assay was carried out by dinitrosalicylic method[14] using 1% starch as substrate at pH 7.0, 50°C for 30 min and optical density was taken at 540nm. The amylase production was determined in IU g^{-1} by applying the standard formula. One unit of enzyme activity was defined as micromoles of glucose released per minute per one gram of substrate.

Inoculum Preparation

The inoculum was prepared by inoculating a single bacterial colony from freshly grown plates into brain heart infusion broth supplemented with 1% soluble starch. The culture was incubated at 37°C, 150 rpm for 24 h and used as inoculum.

Optimization of Amylase Production by Statistical Method

Amylase production from *Bacillus licheniformis* was increased by optimizing the various nutritional and environmental parameters using statistical software Plackett Burman (PB) and Response Surface Methodology (RSM) of the Design Expert version (10.0.7) software (Stat-Ease Corporation, USA).

Selection of Significant Parameters by Plackett-Burman (PB)

A set of 20 experiments was designed using the Plackett-Burman design of the Design expert (version 9.0.7) software (Stat-Ease Corporation, USA) for 11 variables (Table 1) that were analyzed as possible factors affecting production based on literature search. The parameters evaluated were as follows: A: temperature, B: pH, C: time, D: initial moisture content, E: Starch, F : Yeast

Extract, G: Moistening solution, H: inoculum concentration, J: Tween-80, K: NaCl and L: $MgSO_4$. In each experiment, paddy straw was taken as the basal solid media (5g) in 250 ml erlenmyer falsk. Concentration levels were decided on the basis of literature reports on amylase production. Experiments were carried out in triplicates. The average of enzyme activity obtained was taken as response. The effect of individual factors on enzyme activity was calculated according to following equation:

$$E_i = \frac{\sum P_{i+} - \sum P_{i-}}{N} \quad (1)$$

where, E_i is the effect of parameter *i* under study, P_{i+} and P_{i-} are responses (amylase activity) of trials at which the parameter was at its high and low level, respectively, and N is the total number of trials. The significance of the model was calculated by ANOVA. From the pareto chart, the factors showing highest positive effects were selected for optimization using Central Composite Design of Response Surface Methodology.

Central Composite Design (CCD) and Response Surface Methodology (RSM)

Central composite design (CCD) at α value as ± 2 was employed using Design expert software (version 9.0.7, Statease Inc., Minneapolis, USA) to further optimize the levels of significant variables. Amylase activity was recorded as response. Response data were fed and analyzed by the software to generate 3D plots indicating the optimum conditions and interaction among these factors. Regression analysis was performed on the data obtained. A second-order polynomial equation was used to fit the data by multiple regression procedure. This resulted in an empirical model that related the response measured to the independent variables of the experiment.

$$Y = \beta_0 + \Sigma\beta_i X_i + \Sigma\beta_{ii} X_{i2} + \Sigma\beta_{ij} X_i X_j \quad (2)$$

where, Y is the predicted response amylase activity (IU g^{-1}), β_0 is the constant term, β_i the linear coefficients, β_{ii} the squared coefficients and β_{ij} the interaction coefficients. The quality of fitting by the polynomial model equation was expressed using coefficient of determination R^2. Equation 2 was used to construct 3D plots.

Prediction of Optimum Values for Maximum Amylase Production

After getting the model equation that explains the process, it was used for optimization of the amylase production using the numerical optimization option of the software. Criteria were set for each independent variable and the response (dependent variable). The independent variables were kept in the range used by the experimental set up and the response was set maximum. A solution was generated with predicted levels of the independent variables and predicted maximum production.

Validation Experiments

To check the validity of the chosen quadratic model, experiments were designed using the predicted optimum values of the parameters from equation 2. The amylase activity was measured and compared with the predicted value. Each experiment was conducted in triplicates and the data presented as mean ± SD.

Extraction of Amylase

Extraction was done by soaking the fermented solids with 50ml of 0.1M phosphate buffer for 30 min at 30°C on a rotary shaker (150 rpm). The slurry was squeezed through a damp cheese cloth. Suspension was centrifuged at 10000 rpm for 15 min at 37°C to separate small paddy husk particles, cells and spores. Clear Supernatant was collected and further used for amylase assay as per standard method.

RESULT AND DISCUSSION

α-Amylase catalyzes the hydrolysis of internal α-1,4 glycosidic linkages in starch to yield products like glucose and maltose[15]. Due to its hydrolytic action, amylase has been in increasing demand in industries like detergent industry, fuel and alcohol industry, baking industry, textile industry etc. For an enzyme to have industrial application, it must be produced at high level with a relatively cheaper rate. Solid state fermentation is an effective method for the production of enzymes as large amount of enzyme can be produced at relatively cheaper rate using agro-industrial waste which are available free of cost[16].

Paddy straw is a waste obtained from the rice field and is becoming a major problem as its disposal

by burning is a major environmental threat. Earlier we had employed paddy straw for the production of amylase from *Bacillus licheniformis* MTCC 1483 by optimizing various nutritional and environmental parameters using classical one factor at a time approach[13]. OVAT method is quite time consuming and also it does not describe the interaction among the variables[17]. Statistical methods *viz.* placket burman response surface methodology (RSM) are useful tools for increasing the enzyme production as it consumes less time and gives statistical relevant results. Therefore, in this study, PB and RSM approach was used for increasing amylase production from *B. licehniformis* MTCC 1483.

Selection of Significant Parameters using PB

In order to screen the key factors having significant influence on amylase production, a PB experimental design was formulated with 11 different parameters, selected on the basis of literature search and OVAT results. In 12 runs, variation ranging from 785 IUg^{-1} to 3318 IUg^{-1} in the yield of amylase was observed (Table 1). The influence of various parameters on amylase production was estimated and graphically represented in the form of pareto chart (Fig. 1). Length of column represented the significance of the influence of studied parameters on enzyme activity. Out of 11 different parameters tested, eight factors *viz.* Temperature, moisture content, moistening solution, Tween-80, NaCl and starch were found to have positive effect on amylase production. Out of these, starch followed by Tween-80 and moisture content were having maximum effect on enzyme production. The results obtained from the pareto chart were checked by analysis of variance (ANOVA) test for their significance (Table 2). The results confirmed that the model was significant with $p < 0.05$. It was observed that the first three influential parameters were starch concentration, tween-80 concentration and initial moisture level. Increase in amylase production by supplementing the medium with starch is due to the reason that amylase employ starch as substate [18]. The use of surfactants in SsF has been well-documented[19]. Surfactants increase the permeability of the membrane's lipid bilayer, which facilitates the secretion of enzymes[20]. Initial moisture content also plays an important role in SsF[16]. Although, in SsF moisture content of the fermentation medium varies during fermentation due to generation of heat[21], the availability of initial water in lower or higher amounts affects microbial activity adversely[22]. At low moisture level, substrate was not moistened sufficiently to promote the growth of the bacteria while with increase in moisture content above optimum, the porosity of the medium decreased leading to difficulties of oxygen transfer and heat release in the medium[23]. Thus, these three factors were selected for further increase in amylase production by RSM.

Response Surface Methodology

The levels of the three significant parameters which have positive influence on amylase production were used as central values to design experiments for central composite response surface design (Table 3). By applying multiple regression analysis on the experimental data, a predictive quadratic polynomial equation was constructed to describe the correlation between enzyme activity and the three significant parameters as follows:

Amylase yield (IU g-1) = +382.40 - 37.65 * A - 22.42 * B +56.96 * C +16.30 * A* -37.67 * A * C +34.78 * B * C

where, A, B and C were the coded values of time initial moisture level, tween-80 and starch respectively. The analysis of variance for the response surface quadratic model is summarized in Table 4. The p-values <0.05 indicated that the linear, interactive and squared terms, all had quite significant influence on enzyme activity. The p-value for lack of fit was 0.7062, indicating that this quadratic model adequately fit into the data. The maximum enzyme activity of 5086 IU g^{-1} was obtained under conditions *viz.* 1% starch, 1:2 initial moisture content and 0.3% Tween-80.

Individual Effect of Process Parameters on Amylase Production

From the figure 2 it was observed that process parameters A, B and C have significant effects on amylase production. The steep perturbation curve showed that amylase production is highly sensitive to concentration of starch followed by tween-80 and initial moisture content.

Starch is the basic substrate utilized by amylase. Increase in amylase production with the incorporation of starch can be due to the increase in growth of bacteria by directly utilizing the available substrate resulting in increased enzyme production[17]. Tween-80 is known to increase the permeability of the membrane's lipid bilayer, which facilitates the secretion of enzymes[19]. Initial moisture content also plays an important role

Table 1: Plackett Burman design and responses for amylase yield

Run	A:temp degree celsius	B: pH-	C: time h	D: Moisture content %	E: Starch %	F:Yeast extract %	G: Mois-tening Solution-	H: Ino-culum %	J: Tween 80 %	K: NaCl mg	L: MgSO4 %	Amylase yield (IU/g)
1	30.00	6.00	96.00	1:1	0.50	0.50	0.00	20.00	0.30	5.00	0.00	1890.975
2	37.00	8.00	48.00	1:2	0.50	0.50	0.00	10.00	0.00	5.00	0.00	2861.825
3	37.00	8.00	96.00	1:1	0.00	0.00	1.00	10.00	0.30	5.00	0.00	785.8775
4	30.00	6.00	48.00	1:2	0.00	0.50	1.00	10.00	0.30	5.00	0.10	1195
5	37.00	8.00	48.00	1:1	0.00	0.50	0.00	20.00	0.30	0.00	0.10	3086.425
6	30.00	6.00	48.00	1:1	0.00	0.00	0.00	10.00	0.00	0.00	0.00	1021.563
7	37.00	6.00	96.00	1:2	0.50	0.00	0.00	10.00	0.30	0.00	0.10	3898.3
8	30.00	8.00	96.00	1:1	0.50	0.50	1.00	10.00	0.00	0.00	0.10	992.58
9	37.00	6.00	48.00	1:1	0.50	0.00	1.00	20.00	0.00	5.00	0.10	1036.053
10	30.00	8.00	48.00	1:2	0.50	0.00	1.00	20.00	0.30	0.00	0.00	3318.275
11	30.00	8.00	96.00	1:2	0.00	0.00	0.00	20.00	0.00	5.00	0.10	1673.623
12	37.00	6.00	96.00	1:2	0.00	0.50	1.00	20.00	0.00	0.00	0.00	1311.365

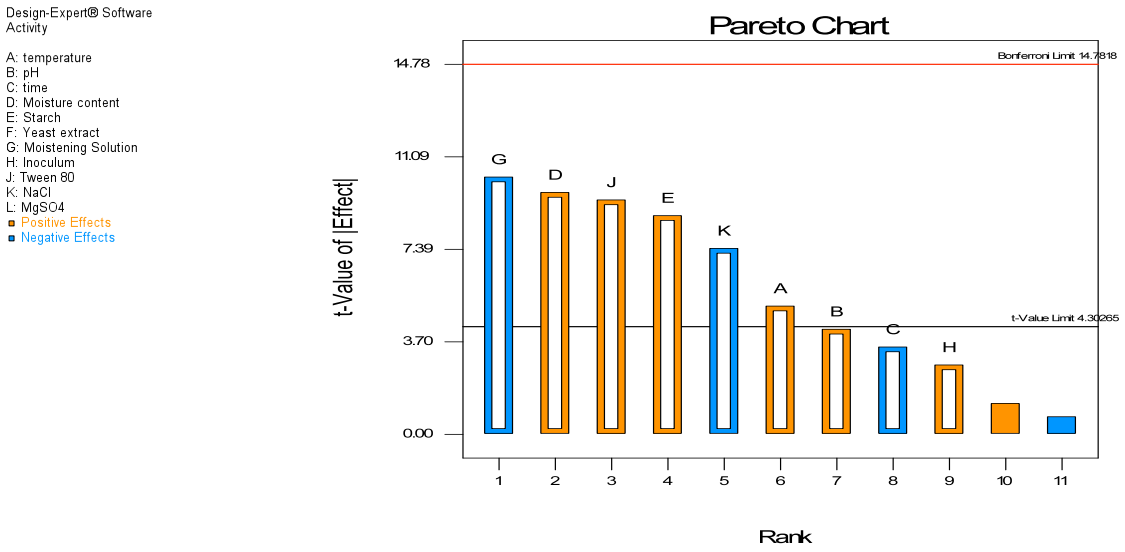


Figure 1: Pareto chart showing factors having positive effects (yellow color) and negative effects (blue color) on amylase production

in SSF[16] For amylase production, initial moisture content of 1:2 was found to be optimum. This can be due to the reason that at low moisture level, substrate was not moistened sufficiently to promote the growth of the bacteria while with increase in moisture content above optimum, the porosity of the medium decreased leading to difficulties of oxygen transfer and heat release in the medium[22].

Table 2: Analysis of variance (ANOVA) for Plackett-Burman Design

Source	Sum of squares	df	Mean Square	F Value	p-value Prob>F	
Model	2.041E+006	9	2.041E+006	53.53	0.0185	significant
A-temperature	1.112E+05	1	1.112E+05	26.25	0.0361	
B-pH	74596.67	1	74596.67	17.61	0.0524	
C-time	51555.73	1	51555.73	12.17	0.0733	
D-Moisture content	3.953E+05	1	3.953E+05	93.31	0.0105	
E-Starch	3.233E+05	1	3.233E+05	76.31	0.0129	
G-Moistening Solution	4.475E+05	1	4.475E+05	105.64	0.0093	
H-Inoculum	32512.47	1	32512.47	7.67	0.1093	
J-Tween 80	3.714E+05	1	3.714E+05	87.67	0.0112	
K-NaCl	2.335E+05	1	2.335E+05	55.13	0.0177	
Residual	8472.83	2	4236.41			
Cor Total	2.05E+06	1				
Std. Dev.	65.09		R-Squared	0.9959		
Mean	769.06		Adj R-Squared	0.9773		
C.V%	8.46		Pred R-Squared	0.8512		
PRESS	3.050E+005		Adeq Precision	20.177		

Table 3: Central composite design with predicted and actual responses

Run	A:Moisture content	B:Tween 80	C:Starch	Yield (IU/g)	Predictive Value (IU/g)
1	3.00	0.65	0.75	3970.32	3824
2	3.00	0.65	0.75	4376.05	3824
3	3.00	1.24	0.75	3723.99	3446.9
4	4.00	1.00	0.50	3202.34	2845.7
5	4.00	0.30	1.00	3839.9	3353.7
6	3.00	0.65	0.75	2419.86	3824
7	4.68	0.65	0.75	3187.85	3190.8
8	2.00	1.00	1.00	5607.7	5107.3
9	2.00	1.00	0.50	2289.45	2519.1
10	2.00	0.30	1.00	5086.07	5186.2
11	4.00	0.30	0.50	3419.69	3663.6
12	3.00	0.06	0.75	4665.85	4201
13	2.00	0.30	0.50	4202.16	3989.1
14	3.00	0.65	1.17	3593.57	4781.9
15	3.00	0.65	0.75	3666.02	3824
16	3.00	0.65	0.75	3999.3	3824
17	3.00	0.65	0.33	2173.53	2866.1
18	1.32	0.65	0.75	4607.98	4457.1
19	3.00	0.65	0.75	4477.48	3824
20	4.00	1.00	1.00	3970.32	3926.9

Table 4: Analysis of variance (ANOVA) for response surface model developed for optimum amylase yield

Source	Sum of squares	df	Mean square	F Value	p-value Prob>F
Model	93682.69	6	15613.78	3.52	0.0272 significant
A-Moisture content	19356.56	1	19356.56	4.36	0.057
B-Tween 80	6865.41	1	6865.41	1.55	0.2356
C-Starch	44304.52	1	44304.52	9.98	0.0075
AB	2126.01	1	2126.01	0.48	0.5011
AC	11355.02	1	11355.02	2.56	0.1338
BC	9675.17	1	9675.17	2.18	0.1637
Residual	57712.52	13	4439.42		
Lack of Fit	29909.54	8	3738.69	0.67	0.7062 not significant
Pure Error	27802.98	5	5560.60		
Cor Total	1.514E+005	19			
Std. Dev.	66.63			R-squared	0.6188
Mean 769.06	382.40			Adj R-squared	0.4429
C.V%	17.42			Pred R- Squared	0.1224
PRESS	1.329E+005			Adeq Precision	6.766

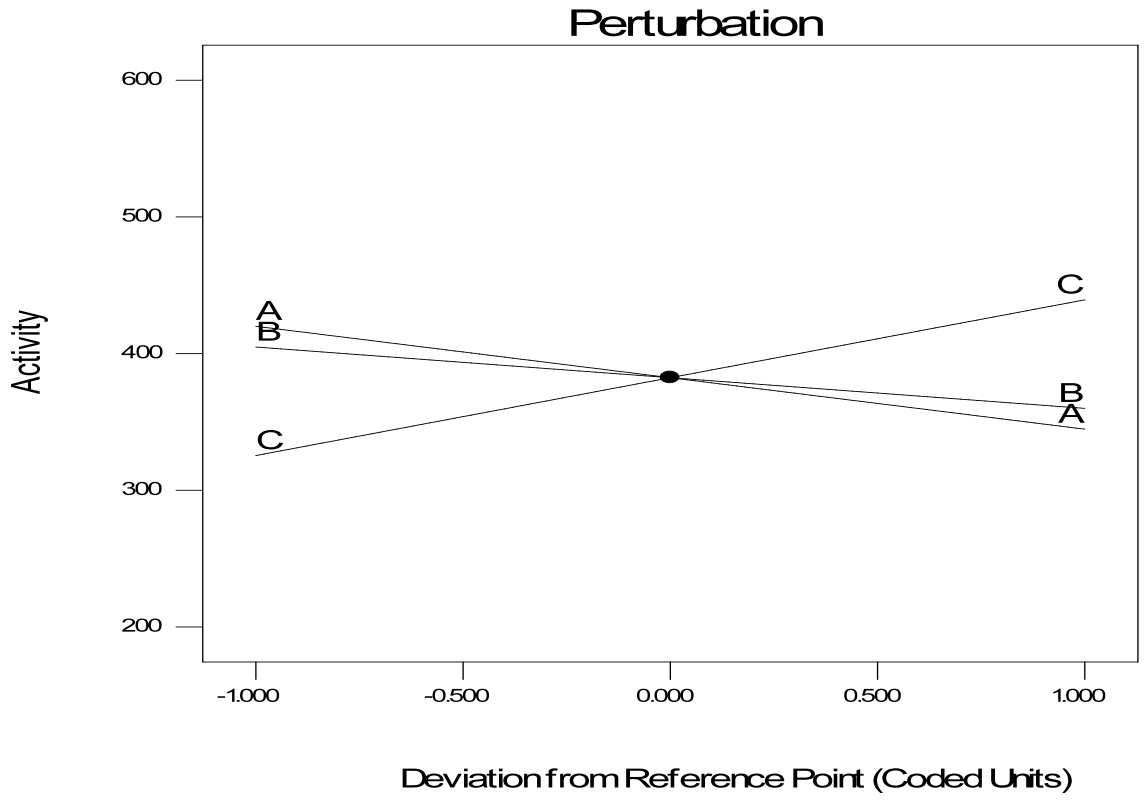
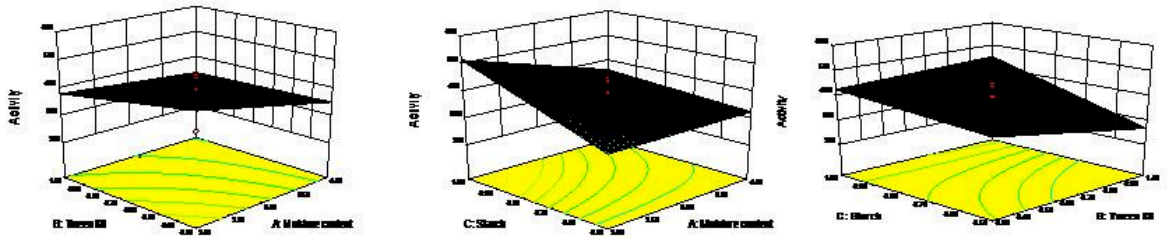


Figure 2: Perturbation graph showing the effect of individual parameters on amylase production



A B C

Figure 3: Three dimensional response curve showing the interactive effect of three parameters (A) Tween-80 and initial moisture content; (B) Fig 3 (B) Starch and initial moisture content; (C) Fig 3 (C) Starch and Tween-80

Table 5: Validation of predicted model

Response (Amylase yield (IU/g)							
Std run	Starch (%)	Initial moisture content	Tween-80 (%)	Actual	Predicted	Residual	Error (%)
1	1.81	1:2.34	0.94	8523 ± 28	8520	3	0.03

Values represent mean ± SD (n=3)

Table 6: Composition of the production medium after optimization of SsF

S.No.	Media component	Quantity
1	Paddy straw	5g
2	Mgso4	0.1%
3	Distilled water	11.7ml
4	tween	0.94(470 µl)
5	starch	1.81%(90.5mg)
6	time	48 hrs
7	pH	8
8	time	48 hrs
9	inoculum	20%(1ml)
10	Initial moisture content	1:2.34 (11.7ml)

Interactive Effect of Process Parameters

The interactive effect of starch, tween-80 and initial moisture content on amylase production was shown in figure 3(a-c). Fig. 3a shows the effect of moisture content and tween 80 on amylase production. It was observed from the curve that increase in moisture content will have negative effect on amylase yield while increase in tween-80 concentration will have positive effect on amylase yield. Similarly, increase in starch concentration will have positive effect on increased amylase production (Fig. 3b, 3c). Thus, amylase production can be increased by increasing the concentration of starch and tween-80 and maintaining the initial moisture content to 1:2.

Validation of Predicted Variables for Maximum Amylase Production

The production parameters were numerically optimized using the software's option. The criteria used for optimization along with predicted and actual (observed) response values are presented in Table 5. The aim was to "maximize" the amylase yield while keeping the three variables level "in range". By using the given criteria a solution i.e. 1.81% starch, 1:2.34 initial moisture content and 0.94% Tween-80, having maximum amylase yield of 8520 IU g-1 was selected and experiments were conducted in triplicate. The observed response was 8523 ± 28 which is very close to the predicted value, thus validating the model. Thus the predicted and actual values are in perfect coherence with each other and thus validated the result. The final composition of the medium is given in Table 6. Thus, an amylase yield of 8523 IUg^{-1} could be achieved under medium optimized in this study in SSF using paddy straw as substrate.

ACKNOWLEDGEMENT

We thank I.K.G. Punjab Technical University, Kapurthala, India for providing support for conduct of research work.

CONFLICT OF INTEREST

The authors declare there is no conflict of interest

REFERENCES

1. Anonymous. (2010) Ministry of Agriculture Ministry of External Affairs Government of India, http://www.indiabusiness.nic.in/economy/agriculture. html, accessed 1 May 2010.
2. Maiorella, B.L. (1985) Ethanol fermentation. In: Young M (ed). *Comprehensive biotechnol*. Pergamon Press, Oxford, Vol 3, pp. 861–914.
3. Jenkins, B.M. and Bhatnagar, A.P. (2003) On electric power potential from paddy straw in Punjab and the optimal size of the power generation station. *Bioresour Technol* 37: 35–41.
4. Wang, J. and Christopher, S.A. (2003) Intercomparison between satellite-derived aerosol optical thickness and PM2.5 mass: Implications for air quality studies. *Geophys Res Lett* 30, 2095–2098.
5. Van Soest, P.J. (2006) Rice straw, the role of silica and treatments to improve quality. *Anim Feed Sci Technol* 130, 137–171.
6. Trivedi, S., Divecha, J. and Shaha, A. (2012) Optimization of inulinase production by a newly isolated Aspergillus tubingensis CR16 using low cost substrates. *Carbohydrate Polymers* 90, 483–490.
7. Pandey, A. and Radhakrishna, S. (1993) The Production of glucoamylase by Aspergillus niger NCIM 1245. *Process Biochem* 28(3): 305–309.
8. Crabb, W.D. and Mitchinson, C. (1997) Enzymes involved in the processing of starch to sugars. *Trends Biotechnol* 15, 349–352.
9. Riaz, A., Ansari, B., Siddiquib, A., Ahmed, S., Naheed, S. and Qader, S.A.U. (2015) Immobilization of α-amylase in operationally stable calcium-alginate beads: A cost effective technique for enzyme aided industrial processes. *Inter J Biotechnol Res* 3(5): 81–86.
10. Soleimani, M., Khani, A. and Najafzadeh, K. (2012) Alpha amylase immobilization on the silica nanoparticles for cleaning performance towards starch oils in laundry detergents. *J Mol Cataysis* 74, 1–5.
11. Ashwini, K., Gaurav, K., Karthik, L. and Bhaskara, R.K.V. (2011) Optimization production and partial purification of extracellular α-amylase from Bacillus sp. Marini Arch. *Appl Sci Res* 3, 33–42.
12. Khan, J.,A. and Yadav, S.K. (2011) Production of alpha amylases by Aspergillus niger using cheaper substrates employing solid state fermentation. *Inter J Plant Animal Environ Sci* 1(3): 100–108.
13. Kaur, P.S., Kaur, S., Kaur, H., Sharma, A., Raj, P. and Panwar, S. (2015) Solid substrate fermentation using agro industrial waste: New approach for amylase production by Bacillus licheniformis. *Int J Curr Microbiol App Sci* 4(12): 712–717.
14. Miller, G.L. (1959) Use of dinitrosalicylic acid reagent for determination of reducing sugar. *Anal Chem* 31, 426–429.
15. Sundarram, A., Pandurangappa, T. and Murthy, K. (2014) α-Amylase production and applications: a review. *J Appl Environ Microbiol* 2(4): 166–175.
16. Bhargav, S., Panda, B.P., Ali, M., and Javed, S. (2008) Solid-state fermentation An Overview. *Chem Biochem Eng, Q* 22(1): 49–70.
17. Sondhi, S., Sharma, P., George, N., Chauhan, P.S., Puri, N. and Gupta, N. (2015) A novel extracellular thermo-alkali-stable laccase from Bacillus tequilensis SN4 having potential to biobleach softwood pulp. *3Biotech 5*, 175–185.
18. Ensari, N.Y., Otludil, B. and Aytekin, M.C. (1995) Effect of starch induced bacterial growth and amylase pro-duction in Bacillus subtilis. *Starch – Starke* 47(8): 315–321.
19. Usha, K.Y., Praveen, K. and Reddy, B.R. (2014) Enhanced production of ligninolytic enzymes by a mushroom. Stereum ostrea 815495.
20. Rao, J.L.U.M. and Satyanarayana, T. (2013) Enhanced secretion and low temperature stabilization of a hyperthermostable and Ca2+- independent a-amylase of Geobacillus thermoleovorans by surfactants. *Lett Appl Microbiol* 36, 191–196.
21. Ibrahim, D. H., Puspitaloka, R., Rahim, A. and Hong, L.S. (2012) Characterization of solid state fermentation culture conditions for growth and mananase production by Aspergillus niger USM F4 on rice husk in tray system. *Br Biotechnol J* 2, 133–145.
22. Hamidi-Esfahani, Z., Shojaosadati, S.A. and Rinzema, A. (2004) Modeling of simultaneous effect of moisture and temperature on A. niger growth in solid-state fermentation. *Biochem Eng J* 21, 265–272.
23. Revankar, M.S., Desai, K.M. and Lele, S.S. (2007) Solid-state fermentation for enhanced production of laccase using indigenously isolated Ganoderma sp. Appl *Biochem Biotechnol* 143, 16–26.

Article

Influence of Biotechnology on Marketing of Building Materials

Jinping Chen
is at the College of Pipeline and Civil Engineering, China University of Petroleum (East China), Qingdao, China

ABSTRACT

Microbial technology as a kind of biotechnology, has a good improvement effect on the performance of building materials and a very large repair effect especially on concrete. From the perspective of biotechnology, the urease produced by microbial metabolism is applied to the formation of calcium carbonate to study its repair effect on building materials - concrete cracks, and its influence on the marketing of building materials. The results show that the microbial induced calcium carbonate can be used to repair the concrete cracks and have good impermeability, and can promote the marketing of building materials.

Journal of Commercial Biotechnology (2017) 23(2), 46–51. doi: 10.5912/jcb791
Keywords: microorganism; MICP technology; concrete; repair; marketing

INTRODUCTION

Biotechnology is a technology that provides processed products or other services through the construction of the expected new substances by the rational use of organisms and their cell and tissue functions combined with engineering principles, taking life science as the core[1]. The ancient people have long applied biotechnology to building materials. Concrete is by far the most widely used building material, with the advantages of low prices, various raw materials and strength in compression. Hence, it will still be a very important kind of building material in the future for a long period of time[2]. Concrete is a typical brittle porous material, containing many pore networks, which will form cracks subjected to internal and external pressure. Besides, unscientific design, unqualified materials, unreasonable mixture ratio and poor construction and maintenance will also lead to concrete cracks[3]. Although the concrete is prone to cracks, it itself can repair the cracks to a certain extent through hydration and carbonation, despite of its weak repair capacity[4]. With the continuous development of science and technology, the means of repairing concrete cracks are also progressing. Nowadays, surface treatment, deposition and grouting are commonly used for the remediation of concrete[5]. Courtyard L et al[6] changed the concrete form through the patch repair and increasing the surface roughness of the concrete. Wu H et al[7] used chemical grouting method to repair the cement concrete pavement cracks, and achieved good results. Sen L L et al[8] used electrodeposition to study the repair of cracks and discussed the existing problems and future research directions. Concrete building materials is a kind of product which draws little public attention and belongs to the scope of durable goods. Hence, the marketing strategy for the product is difficult to develop. In this paper, the Microorganism Induced Calcite Precipitation (MICP) technology is used to repair the cracks of the concrete and the results show that the MICP technique could effectively repair the cracks of concrete and promote the marketing of concrete materials.

Correspondence:
Jinping Chen, China University of Petroleum(East China), China. Email: chenjp@upc.edu.cn

MICP TECHNOLOGY

Studies have shown that when some microorganisms in the soil are in a particular nutrient environment, they will speed up their metabolism and rapidly precipitate mineral crystals such as carbonates through degradation, leading to the increase in the concentration of inorganic carbon and PH value in the environment. When in an alkaline environment, the soluble inorganic carbon undergoes hydrolysis, forming CO^{2-}_3. While the microbial cell wall is with negative charge and will adsorb positive charge such as Ca^{2+} in the neutral environment and

then produce $CaCO_3$ after reacting with $CO^{2-}{}_3$, followed by sediment, which is called the MICP technology[9-10]. The basic principle formulas are as follows:

$$CO(NH_2)_2 + H_2O \rightarrow NH_2COOH + NH_3 \quad (1)$$

$$NH_2COOH + H_2O \rightarrow NH_3 + H_2CO_3 \quad (2)$$

$$CO(NH_2) + H_2O \rightarrow CO_3^{2-} + 2NH_4^+ \quad (3)$$

$$Ca^{2+} + Cell \rightarrow Cell\text{-}Ca^{2+} \quad (4)$$

$$Cell\text{-}Ca^{2+} + CO_3^{2-} \rightarrow Cell\text{-}CaCO_3 \downarrow \quad (5)$$

Urease produced by microorganisms can accelerate the hydrolysis of urea, thus forming ammonia and carbonic acid. The negative charge of the cell wall is constantly reacting with Ca^{2+} and precipitates calcium carbonate crystals through mineralization with carbonate ions. Overbased microbes are mainly responsible for providing urease, and produce carbon dioxide and oxygen through the urease reaction and respiration action, to provide the location of calcium carbonate precipitation.

EXPERIMENTAL STUDY

Preparation of Culture Medium

The Bacillus bacillus (purchased from Ruigu Biotechnology Co., Ltd., Baoding, Hebei.) is selected as the microorganism in this study. In order to make the growth of the Bacillus bacillus better, a medium suitable for its growth was prepared, as follows: firstly, 30 g of 20 g / L yeast extract (purchased from Bei Nai Bio Co., Ltd.), 15 g of ammonium sulfate at a concentration of 10 g / L (purchased from Changzhou LanYa New Material Technology Co., Ltd.) and 3.5 g of nickel chloride at a concentration of 10 umol / L (purchased Baoding Fusai cobalt-nickel New Materials Co., Ltd.) were put into a pure water beaker and added with water to 1500 ml after full dissolution. Then, the pH value was adjusted to 9 with NaOH solution. After sterilization, the cells were inoculated and placed in a shaking incubator (Shanghai Guan Sen Biotech Co., Ltd.) at 30 ° C and 150 r / min for 24h.

Urease Activity Detection

The urease produced by bacteria is the key to the experiment, so there is need for its activity detection, to make the experiment to proceed smoothly. 5 ml of the bacterial solution was mixed with 30 ml of 1.1 mol / L urea solution, the temperature was adjusted to 25 °C, and the conductivity change of the solution within 5 minutes was measured with a conductivity meter (METTLER TOLEDO, Switzerland). The urease activity (mS / cm / min) was obtained by multiplying the average change in conductivity by the dilution factor of the bacterial solution.

Initial Detection of MICP Deposition

Nine concrete specimens were prepared and each concrete specimen was 20 cm x 10 cm x 10 cm in size. The fracture size and calcium source in each specimen are shown in the following table:

1. 200mL of bacterial liquid and 300mL of calcium source were drip irrigated to each concrete specimen crack, as shown in Figure 1. The drip irrigation temperature was maintained at 30 °C, and the speed was 75 drops / min for bacterial liquid and 100 drops / min for calcium source.
2. After the drip irrigation was completed, the equipment was removed and the cracks were cut and observed.
3. The liquid in the glass tank was excluded and the glass tubes on both sides of the glass tank were closed; water was injected and the controller was adjusted to the maximum. Timing was started when there was liquid overflowing above the glass tank on the discharge side. The detection time was 30 min, and the amount of the discharged liquid and the height of the sediment on the injection side were recorded.
4. The results of water infiltration before and after 2, 4, 8 and 16 times of drop irrigation were recorded and the impermeability was tested.
5. The orthogonal test was carried out on the nine specimens to calculate the range. The greater the difference, the greater the impact.

Experimental Results

Calcium carbonate changes with various depths

It can be seen from Fig. 2 that the deposition of CaCO3 increased first and then decreased with the increase of depth. At 90mm, the deposition of calcium carbonate was the largest. This is because that the water was more

Table 1: Crack and calcium source situation

Number	Crack width (mm)	Crack depth (mm)	Calcium source	With or without oxygen
1	A(0.5)	A(50)	A(Calcium chloride)	A(without oxygen)
2	A(0.5)	B(100)	B(Calcium nitrate)	B(with oxygen
3	A(0.5)	C(150)	C(Calcium acetate)	C
4	B(1)	A(50)	B(Calcium nitrate)	C
5	B(1)	B(100)	C(Calcium acetate)	A(without oxygen)
6	B(1)	C(150)	A(Calcium chloride)	B(with oxygen)
7	C(1.5)	A(50)	C(Calcium acetate)	B(with oxygen)
8	C(1.5)	B(100)	A(Calcium chloride)	C
9	C(1.5)	C(150)	B(Calcium nitrate)	A(without oxygen)

Among which, the calcium source concentration was 2 mol / L.

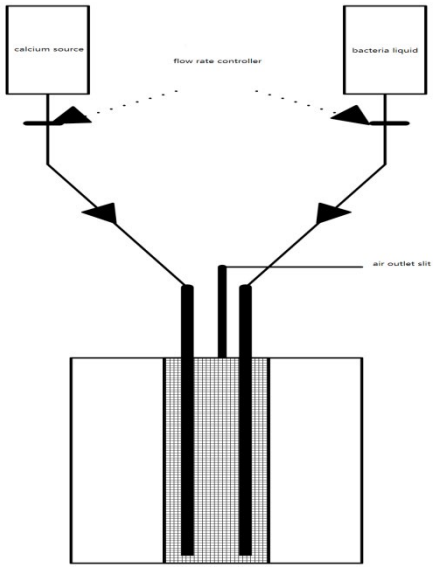


Figure 1: Drip irrigation schematic diagram

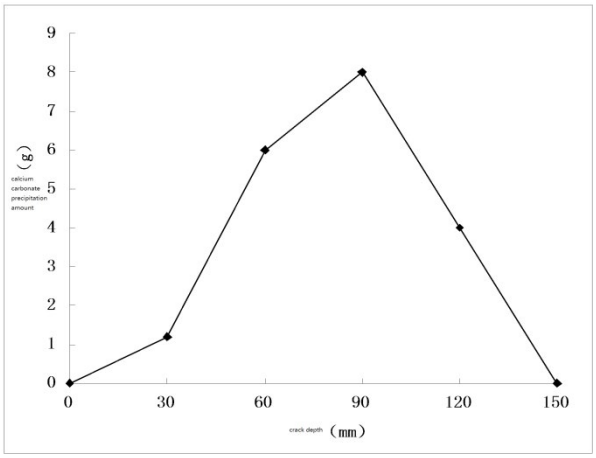


Figure 2: Deposition of calcium carbonate with increasing depth

turbulent on both ends of the inlet and outlet with larger impact effect which was not conducive to the deposition of calcium carbonate crystals while the water flow in the middle part was more slowly and presented a laminar flow state which was good for the deposition of calcium carbonate crystals.

Impact of different drop irrigation time on water percolating capacity

From figure 3, we can see that with the increase of the number of irrigation, the amount of water seepage decreased gradually. For the precipitation height of the glass tank, the greater the number of irrigation was, the higher the precipitation would be. Thus, we can conclude that the higher the calcium carbonate precipitation in the crack, the smaller the crack width and the cross-sectional area, leading to the continuous reduction of water seepage. The results of the impervious performance experiment show that the maximum impervious water pressure of all the nine specimens was above 0.05Mpa, which means that the repaired concrete could bear at least 5m water pressure, which meets the requirements of general underground construction.

Orthogonal analysis on different crack sizes and calcium sources

In Table 1, we divided the cracks and the calcium sources of the concrete specimens. The experimental results show that the experimental results of No.1 to No.6 are 22,21,22,20,20,17,19, 18 and 15 respectively. The quadrature mean values are shown in the following table:

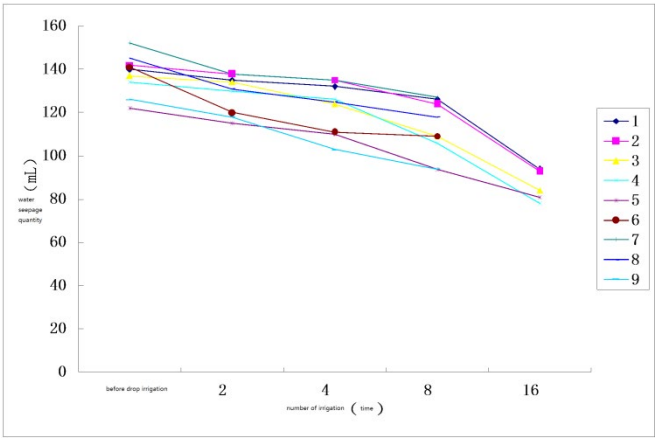


Figure 3: Impact of different drop irrigation time on water percolating capacity

Table 2: Orthogonal analysis of mean data

Number	Crack width (mm)	Crack depth (mm)	Calcium sources	With or without oxygen
A	21.67	20.33	19	19
B	19	19.67	18.67	19
C	17.33	18	20.33	20
Range	3.10	1.70	1.24	0.82

We can see from table 2 that the main factor among the four factors is the crack width and the second factor is the crack depth, followed by calcium source, and the final one is whether there is oxygen or not. Among the mean values of crack width, A>B>C (A, B and C represents 0.5mm, 1 mm and 1.5 mm respectively), suggesting that the smaller the width of the crack, the more likely it is to be repaired. Similarly, for the mean values of crack depth, A>B>C, suggesting that the smaller the depth of the crack, the more likely it is to be repaired. For the mean values of calcium source, C>A>B (C, B and A represents calcium acetate, calcium chloride and calcium nitrate respectively), suggesting that calcium acetate can promote the formation of calcium carbonate. Finally, whether there is oxygen or not does not have obvious impact on the effect of repairing.

CHANGES OF MARKETING MODE

With the rapid economic development, China has become one of the world's largest building materials market. Traditional building materials' marketing is realized through television, radio, newspapers and magazines[11]. With the development of the network, building materials' marketing is gradually stepping into the network marketing. Online marketing sends the purchased material to the purchaser's destination via an online payment. But because buyers do not personally contact with the building materials, there are often quality problems and other related issues. There is no place for concrete in online marketing, which is prone to cracks, though in great demand.

It is conductive to the online marketing of the concrete to repair its cracks and improve its performance as well as its quality through the microbial technology. Not only that, for buyers who come to the factory personally, the quality of the building materials can be highlighted[12]. General building materials' marketing includes marketing communications, such as word of mouth and professionals led, price strategy, price reduction, for example, and public relations strategy, such as holding knowledge lectures on building materials. These marketing modes do have their own advantages, still, deficiencies exist. For example, the purpose of price strategy is to realize quick returns and small margins. However, as mentioned above, building materials are different from other products and price reduction will not lead to sales rise and can even cause a drop on sales. It comes to a conclusion that there is a lack of marketing on the quality of building materials. Durable product itself is an existence with marketing difficulty and customers tend to pay more attention to its quality during purchasing. Therefore, the MICP technology is recommended to a local concrete building material factory in this experiment. Through

the concrete crack repair technology publicity and uploading the compression test video to the company's home page, the sales of concrete within a quarter showed an increase of 20% over last year and the concrete was even sold to other provinces.

It is a key step to convert the emphasis of the marketing of building materials from price to quality. The use of MICP technology in building materials improves the performance of building materials as well as their competitiveness, which makes the building materials better meet the requirement of the building material industry and widens their market. Therefore, the use of the MICP technology has a great positive impact on the marketing of building materials.

CONCLUSION

Biotechnology mainly includes genetic engineering, cell engineering, fermentation engineering and enzyme engineering[13]. In this paper, enzyme engineering was applied. The urease produced by the microbial life activities was applied to a series of relevant reactions, which finally produced calcium carbonate. From the experiment, there was more deposition of calcium carbonate in the lower part of the cracks. As the cracks were gradually repaired, the density of the middle and lower part was higher than that of the upper part. Microorganisms are the main influencing factors of calcium carbonate deposition. According to relevant studies, when the microbial activity was high, the blocking rate of concrete cracks was greater. Therefore, the activity of micro-organisms should be ensured[14]. Besides, it is also found from the experiment that crack width has the deepest impact on the repair effect, followed by crack depth, calcium source and whether there is oxygen or not. Therefore, in actual work, the cracks with small width and depth and with calcium acetate as the calcium source can be repaired most easily. Through drop irrigation on the concrete for several times, it is found that the larger the number of irrigation, the less the water seepage. Therefore, it is concluded that the MICP technology has a good repair effect not only on the exterior environment of the concrete but also on the internal structure of the concrete. With the help of this technology, the marketing mode and marketing market of a local concrete building materials factory were further optimized and expanded. Due to time constraints and other factors, this paper does not study the other factors, which still need improvement in future studies. In summary, biotechnology can improve the performance of building materials, and plays an important role in promoting its marketing.

This work is funded by the project of The Reason and Countermeasure of House Price Rise in the 21 Century, supported by the Science and Technology Department of Henan Province (Number: 112400430131), held by Lei Jiao.

REFERENCES

1. Hilgartner, S. (2015) Biotechnology. *International Encyclopedia of the Social & Behavioral Sciences* 10(1): 1235–1240.
2. Zdeněk P. Bažant and Gambarova, P.G. (2015) Crack shear in concrete: Crack band microflane model. *Journal of Structural Engineering* 110(9): 2015–2035.
3. Larrard, F.D. (2016) Concrete mixture proportioning. *Information Storage & Retrieval* 4(2): 113–131.
4. Tittelboom, K.V., Maes, M. and Belie, N.D. (2014) Can self-repair of concrete cracks help to obtain durable concrete? Concrete Solutions. CRC Press/Balkema, 121–125.
5. Hou Hongyan. (2015) Analysis of concrete crack and application of chemical grouting in crack treatment and calculation method of cost. *Cement Grinding Aid and Concrete Admixture* (1): 54–56.
6. Courard, L., Piotrowski, T. and Garbacz, A. (2014) Near-to-surface properties affecting bond strength in concrete repair. *Cement & Concrete Composites* 46(4): 73–80.
7. Wu, H., Zhu, M., Liu, Z. and Yin, J. (2015) Introduction of a Chemical Grouting Method for the Crack Repairing of Asphalt Pavements. International Symposium on Systematic Approaches to Environmental Sustainability in Transportation, 77–86.
8. Sen lin, L.I., Qing fa, L.U., Ning, X.U. and Jing, N. (2013) Research progress and direction of electro-deposition method for repair of concrete cracks. *Concrete* 34(2): 139–142.
9. Kleiber, T., Starzyk, J. and Górski, R. et al. (2014) The studies on applying of Effective Microorganisms (EM) and CRF on nutrient contents in leaves and yielding of tomato. Acta scientiarum Polonorum. *Hortorum cultus* = *Ogrodnictwo* 13(2014): 79–90.
10. Qabany, A.A. and Soga, K. (2013) Effect of chemical treatment used in MICP on engineering properties of cemented soils. *Géotechnique* 63(4): 331–339.
11. Xu Haiping. (2012) Talking about the green environmental protection trend of building materials in China. *Building Materials & Decoration* (19): 108–108.

12. Xiao Bin. (2015) Self - repairing of concrete cracks based on microbial technology. *Technology and Market* (7): 235–237.

13. Dudley, Q.M., Karim, A.S. and Jewett, M.C. (2015) Cell free metabolic engineering: Biomanufacturing beyond the cell. *Biotechnology Journal* 10(1): 69–82.

14. 14. Erşan, Y.Ç., Hernandez-Sanabria, E. and Boon, N. et al. (2016) Enhanced crack closure performance of microbial mortar through nitrate reduction. *Cement & Concrete Composites* 70: 159–170.

Article

Product Hopping

Michael A. Carrier

is Distinguished Professor at Rutgers Law School. He is a leading authority in antitrust and intellectual property law with expertise in the pharmaceutical, high-technology, and music industries. Professor Carrier is a co-author of the leading IP/antitrust treatise, IP and Antitrust Law: An Analysis of Antitrust Principles Applied to Intellectual Property Law (3d ed. 2017, with Hovenkamp, Janis, Lemley, and Leslie). He also is the author of Innovation for the 21st Century: Harnessing the Power of Intellectual Property and Antitrust Law (Oxford University Press 2009, paperback 2011) and the editor of Critical Concepts in Intellectual Property Law: Competition (Edward Elgar Publishing 2011).

ABSTRACT

One of the most pressing issues in antitrust law involves "product hopping." A brand-name pharmaceutical company switches from one version of a drug (say, capsule) to another (say, tablet). The concern with this conduct is that some of these switches offer only a trivial medical benefit but significantly impair generic competition. The antitrust analysis of product hopping is nuanced. In the U.S., it implicates the intersection of antitrust law, patent law, the Hatch-Waxman Act, and state drug product selection laws. In fact, the behavior is even more complex because it involves uniquely complicated markets characterized by buyers (insurance companies, patients) who are different from the decision-makers (physicians). This article introduces the relevant U.S. laws and regulatory frameworks before exploring the five litigated cases.

Portions of this article are adapted from Michael A. Carrier & Steve Shadowen, *Product Hopping: A New Framework*, 92 NOTRE DAME L. REV. 167 (2016)

Journal of Commercial Biotechnology (2017) 23(2), 52–60. doi: 10.5912/jcb795

PRODUCT HOPPING

Product hopping (also called "evergreening" or "line extension") refers to a drug company's reformulation of its product and encouragement of doctors to prescribe the reformulated, rather than original, product. A brand manufacturer engages in a "product hop" by combining two actions: (1) reformulating the product in a way that makes a generic version of the original product not substitutable and (2) encouraging doctors to write prescriptions for the reformulated rather than the original product, *i.e.*, switching the prescription base from the original to the reformulated product.

There are several types of reformulations, which the first section catalogs. The next two sections introduce the foundations of the regulatory regime: the Hatch-Waxman Act and state substitution laws. The final section then focuses on a crucial element of pharmaceutical competition: the timing of the brand's reformulation in relation to generic entry.

Forms

Product hopping occurs through one (or more than one) of several types of reformulations. One category involves new forms, which consist of switches from a capsule, tablet, injectable, solution, suspension, or syrup to another form, such as any of the above, as well as extended-release capsules or tablets, orally dissolving tablets, and chewable tablets.[1] For example, the makers of antidepressant Prozac and cholesterol treatment TriCor switched from capsule to tablet form, while anxiety-treating Buspar was switched from tablet to capsule.[2]

A second type of reformulation involves changing molecule parts (known as "moieties") by adding or removing compounds. More technically, a manufacturer can switch from one "enantiomer" (one of a pair

Correspondence:
Michael A. Carrier, Rutgers Law School, US. Email: mcarrier@law.rutgers.edu.

1 Steve Shadowen et al., *Anticompetitive Product Changes in the Pharmaceutical Industry*, 41 Rutgers L.J. 1, 24 (2009).

2 *Id*. at 37.

of chemical compounds that has a mirror image) to another.[3] For example, and foreshadowing the change discussed below from heartburn-treating Prilosec to Nexium, a manufacturer can switch from a chemical compound that is an equal mixture of each enantiomer, only one of which contains the active ingredient, to a compound that includes only the enantiomer with the active ingredient.[4] Chemical changes also explain the switches from allergy medication Claritin to Clarinex, antidepressant Celexa to Lexapro, and heartburn medication Prevacid to Kapidex.[5]

A third category of reformulation involves a combination of two or more drug compositions that had previously been marketed separately.[6] Combinations have involved migraine-treatment Treximet (combining Imitrex and Naproxen Sodium) and high-blood-pressure medications Azor (Norvasc and Benicar), Caduet (Norvasc and Lipitor), and Exforge (Norvasc and Diovan).[7]

Hatch-Waxman Act

A crucial element of the regulatory framework forming the backdrop of product hopping is the Hatch-Waxman Act, enacted by Congress in 1984 to increase generic competition and foster innovation in the pharmaceutical industry.[8]

The Act fostered generic competition by creating a new process for obtaining U.S. Food and Drug Administration (FDA) approval, encouraging generics to challenge invalid or noninfringed patents by introducing a 180-day period of marketing exclusivity for the first generic to do so, and resuscitating a defense that allowed generics to experiment on a brand drug during the patent term.[9] The drafters of the Act sought to ensure the provision of "low-cost, generic drugs for millions of Americans,"[10] and recognized that generic competition would save consumers, as well as federal and state governments, millions of dollars each year.[11]

One central goal of the Act was to promote generic competition. Generic drugs have the same active ingredients, dosage, administration, performance, and safety as patented brand drugs.[12] Despite the equivalence, generic manufacturers were required, before the Act, to engage in lengthy and expensive trials to demonstrate safety and effectiveness. The FDA approval process took several years, and because the required tests constituted infringement, generics could not begin the process during the patent term.[13] They therefore waited until the end of the term to begin these activities, which prevented them from entering the market until two or three years after the patent's expiration. At the time Congress enacted Hatch-Waxman, there was no generic equivalent for roughly 150 drugs whose patent term had lapsed.[14]

In the Act, Congress employed several mechanisms to encourage competition. First, it allowed firms to experiment on the drug during the patent term. In particular, the legislature exempted from infringement the manufacture, use, or sale of a patented invention for uses "reasonably related to the development and submission of information" under a federal law regulating the manufacture, use, or sale of drugs.[15]

Second, the Act provided 180 days of marketing exclusivity to the first generic to challenge the brand's patent or claim that it did not infringe the patent. Such exclusivity was reserved for the first generic firm—known as a "Paragraph IV filer"—that sought to enter during the patent term.[16] During the period, which begins after the first commercial marketing of the drug,

3 *Enantiomer*, MerriamWebster, http://www.merriam-webster.com/dictionary/enantiomer (last visited Dec. 2, 2015).

4 Shadowen et al., *supra* note 1, at 24.

5 *Id*. at 38.

6 *Id*. at 25.

7 *Id*. at 39-41.

8 Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended at 21 U.S.C. § 355).

9 Michael A. Carrier, *Unsettling Drug Patent Settlements: A Framework for Presumptive Illegality*, 108 Mich. L. Rev. 37, 42-43 (2009).

10 130 Cong. Rec. 24427 (1984) (statement of Rep. Waxman).

11 *Id.*

12 U.S. Dep't of Health & Human Servs., Food & Drug Admin., *Generic Drugs: Questions and Answers* (2015), http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100.htm.

13 Congressional Budget Office, How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry 38 (1998).

14 H.R. Rep. No. 98-857, pt. 1, at 17 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2650. *See generally* Carrier, *supra* note 9, at 42.

15 35 U.S.C. § 271(e)(1)(2004).

16 21 U.S.C. § 355(j)(5)(B)(iv). Three other patent certifications apply if the drug is not patented, the patent has expired, or the generic agrees it will not seek approval until the patent expires. 21 U.S.C. § 355(j)(2)(A)(vii).

the FDA cannot approve other generic applications for the same product.[17]

Third, and most relevant for our purposes, Congress created a new process for obtaining FDA approval. Before Hatch-Waxman, generic firms that offered products identical to approved drugs needed to independently prove safety and efficacy.[18] One reason that generics chose not to bring products to the market after a patent's expiration was the expense and time involved in replicating clinical studies. The Act created a new type of drug application, called an Abbreviated New Drug Application (ANDA), that allowed generics to rely on brands' safety and effectiveness studies, dispensing with the need for lengthy and expensive independent preclinical or clinical studies.[19]

In short, faced with the problem of insufficient generic entry and high drug prices, Congress enacted legislation that introduced several industry-shaping mechanisms to encourage generic entry.

State Drug Product Selection Laws

States also have made it easier for generics to reach the market through their enactment of drug product selection (DPS) laws. Such laws, in effect in all 50 states today, are designed to lower consumer prices.[20] The laws allow (and in some cases require) pharmacists—absent a doctor's contrary instructions—to substitute generic versions of brand-name prescriptions.

DPS laws are designed to address the price disconnect in the industry between prescribing doctors, who are not directly responsive to drug pricing, and paying insurers and consumers, who do not directly select the prescribed drug.[21] In particular, they carve out a role for pharmacists, who are much more sensitive to price than are doctors.[22] Doctors are subject to a vast array of drug promotion, which includes detailing (sales calls to doctor's offices), direct mailings, free drug samples, medical journal advertising, sponsored continuing medical education programs, and media advertising.[23] Pharmacists, in contrast, make greater margins on generics and recommend them to consumers,[24] competing with other pharmacies on price.[25]

The DPS laws typically allow pharmacists to substitute generic versions of brand drugs only if they are "AB-rated" by the FDA. This is a safety regulation, unconcerned with and unresponsive to the requirement's effect on competition. To receive an AB rating, a generic drug must be therapeutically equivalent to the brand drug, which means that the generic has the same active ingredient, form, dosage, strength, and safety and efficacy profile.[26] The drug also must be bioequivalent, which signifies that the rate and extent of absorption in the body is roughly equivalent to the brand drug.[27]

Product-hopping schemes take advantage of this regulation. By making minor changes to the original product—for example, switching from a capsule to a tablet, or from a 10-mg to a 12-mg dose—the brand can prevent the generic from obtaining the AB rating the generic needs to be substituted for the brand. After the brand's reformulation, the generic cannot be substituted for the new version—to become substitutable it must start the FDA approval process all over again. And while the generic may eventually obtain an AB rating to the reformulated product, such a showing likely will not occur for years as the generic reformulates its product,

17 Federal Trade Commission, Generic Drug Entry Prior to Patent Expiration: An FTC Study 7, https://www.ftc.gov/sites/default/files/documents/reports/generic-drug-entry-prior-patent-expiration-ftc-study/genericdrugstudy_0.pdf [hereinafter FTC, Generic Drug Study]. Until amended in 2003, the Hatch-Waxman Act included as a second trigger for the 180-day period a court decision finding invalidity or lack of infringement.

18 Elizabeth Stotland Weiswasser & Scott D. Danzis, *The Hatch-Waxman Act: History, Structure, and Legacy*, 71 Antitrust L.J. 585, 588 (2003).

19 FTC, Generic Drug Study, *supra* note 18, at 5.

20 *See, e.g.*, Norman V. Carroll et al., *The Effects of Differences in State Drug Product Selection Laws on Pharmacists' Substitution Behavior*, 25 Med. Care 1069, 1069 (1987).

21 Drug Product Selection, Staff Report to the FTC 2-3 (1979).

22 Alison Masson & Robert L. Steiner, Generic Substitution and Prescription Drug Prices: Economic Effects of State Drug Product Selection Laws 7 (1985).

23 Stuart O. Schweitzer, Pharmaceutical Economics and Policy 87-93 (2d ed. 2007).

24 Shadowen et al., *supra* note 1, at 16, 45-48.

25 Masson & Steiner, *supra* note 24, at 7. *See generally* Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 Fla. L. Rev. 1009, 1017-18 (2010).

26 Center For Drug Evaluation and Research, FDA, U.S. Department of Health and Human Services, *Orange Book Preface: Approved Drug Products with Therapeutic Equivalence Evaluations* (29th ed.), http://www.fda.gov/drugs/developmentapprovalprocess/ucm079068.htm; Shadowen et al., *supra* note 1, at 5.

27 *Id.*

seeks FDA approval, and typically files a Paragraph-IV certification, which tends to be followed by the brand's automatic "30-month stay" of FDA approval and additional delays from patent litigation.[28] All of these delays prevent the effective operation of the DPS laws, removing the role of pharmacists and depriving consumers of the practical opportunity to consider a lower-priced generic version of the drug.

Timing of Generic Entry

A seminal event in the lifecycle of a prescription drug is generic entry. When multiple generics enter the market, the price falls to a fraction of the brand price.[29] Brand firms thus have every incentive to delay the entry of generic competition as long as possible.

The dramatic effects of generic entry explain the crucial role played by the Hatch-Waxman Act and state DPS laws. And they shed light on the essential element, in the product-hopping context, of the timing of generic entry. Stated most simply, the brand firm will be much more successful in forestalling generic competition if it can switch the market to the reformulated drug *before* a generic of the original product enters the market.

The reason is that if the brand can migrate the market to the reformulated version, then the heavy promotion and marketing artillery at its disposal can convince doctors to prescribe this drug. The fact that consumers can substitute a generic for the old version of the drug is not of practical significance given that doctors would tend to prescribe the reformulated version.

Stated more technically, introducing the reformulated product before generic entry ensures that not only will there be almost no competition on price but also that there will be almost no competition on quality.[30] Before generic entry, brands offer an uncontested message of the new product's superiority as their detailers extol the new product at a time when no one is praising the original.[31] Brands make the switch when doctors may not even be aware that a generic alternative is forthcoming.[32]

Several examples demonstrate the crucial role of timing. In the *TriCor* case discussed below, the brand firm predicted that it would sell more than *ten times* as many tablets if it was able to switch doctors to the reformulated product before the generic version of the original product entered the market.[33] Another example involved a confidential analysis of a product for which projected sales would be *three times* higher if the reformulation (replacing a twice-daily version with a once-a-day version) occurred two years before the generic of the original product entered the market.[34] Another brand firm acknowledged that its reformulation was "a gimmick" and that switching the market before generic entry was the "cardinal" factor of success.[35] Similar testimony in a different case referred to a "[t]otal [d]isaster" if the reformulated product was introduced after the generic of the original product entered the market.[36] The brand's internal documents in the hearing in the *Namenda* case discussed below revealed that "if we do the hard switch and [] convert patients and caregivers to once-a-day therapy versus twice a day, it's very difficult for the generics then to reverse-commute back."[37] And a recent empirical review of product hops concluded that "after a patient is on the new drug and the old drug has gone generic, the new brand did not lose share," which was true "regardless of clinical differentiation."[38]

The importance of timing also was recognized by the European Commission, which addressed obstacles blocking generic entry in its Pharmaceutical Sector Inquiry Final Report.[39] The report concluded that brands would suffer reduced sales and prices if generics entered the market before or at the same time as the reformulated product.[40] For that reason, brands viewed it as "of the utmost importance" to "bring the follow-on product

28 Carrier, *supra* note 27, at 1017-18.

29 *About FDA: Generic Competition and Drug Prices, U.S. Food & Drug Admin.*, http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm (last visited Dec. 2, 2015). *See generally* F. Morton & M. Kyle, *Markets for Pharmaceutical Products*, in II Handbook of Health Economics 792-93 (M. Pauly et al., eds. 2012) (summarizing recent studies on generic penetration rates and prices).

30 Shadowen et al., *supra* note 1, at 51.

31 *Id.*

32 *Id.* at 35.

33 *Id.* at 52.

34 *Id.* at 53.

35 *Id.*

36 Meijer, Inc. v. Barr Pharmaceuticals, Inc., 572 F. Supp. 2d 38, 43 (D.D.C. 2008).

37 New York v. Actavis (*Namenda*), 787 F.3d 638, 656 (2d Cir. 2015).

38 Aaron Gal, *Why Does Lifecycle Management Still Work?*, at 3 (Bernstein Research June 14, 2013).

39 European Commission, Pharmaceutical Sector Inquiry Final Report ¶ 3 (2009), http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/staff_working_paper_part1.pdf.

40 *Id.* ¶ 1010.

on the market before the first product effectively loses exclusivity."[41]

The brand firm facilitates such a switch by "channeling demand from the first product to the follow-on product" and by "delay[ing] or prevent[ing] generic entry for the sensitive period of the product switch."[42] For 13 of the 22 second-generation products discussed in the report, the new product was launched before the first lost exclusivity, with an average lead time of 17 months.[43]

The report included several telling comments from drug companies. One explained that "the switch rate is dramatically reduced" if generics enter at the time of, or before, the introduction of the second-generation product.[44] Similarly, as another brand revealed: "Each patient that is not switched quickly enough" to the second-generation product is "forever lost to the generics."[45] In contrast, as a third conceded, "[o]nce the patient is switched" to the reformulated product, "the physician does not have to, cannot, and will not switch him to a generic," and "more important, the pharmacist cannot substitute!!"[46]

In short, the timing of reformulation is a crucial factor in a brand's ability to switch the market to a reformulated drug. As discussed in the next section, courts have not always focused on this issue.

JUDICIAL ANALYSIS

Given the complexity of the relevant economics and market structure, it is not a surprise that judicial analysis of product hopping in the U.S. has varied widely. Just as important, the timing of the cases has shaped the development of the law. In particular, the factual settings of the first two cases set the stage for the analysis in later cases.

The first section begins with *TriCor*, in which the court offered a nuanced analysis, albeit one that later courts restricted to "hard switches" (in which the brand firm removes the old product from the market). The next section discusses the *Walgreen* case, which addressed a "soft switch" (in which the brand leaves the original product on the market) and offered a simplistic version of consumer choice.

The court in the *Suboxone* case, addressed in the following section, revealed aspects of both hard and soft switches, with the court offering a nuanced understanding of the regulatory regime. The *Mylan* case addressed in the succeeding section, in contrast, failed to fully appreciate the regime. And the *Namenda* opinion, addressed in the final section, understood the regulatory regime in the context of hard switches, but overemphasized the distinction between hard and soft switches and introduced a new, underinclusive framework based on coercion.

TriCor: Hard Switch, Nuanced Analysis

In *Abbott Labs v. Teva*, the Delaware district court provided the first analysis of product hopping.[47] It considered Abbott's series of changes to its billion-dollar cholesterol and triglycerides drug TriCor. Abbott marginally lowered the drug's strength, switched from a capsule to a tablet, stopped selling capsules, bought back existing supplies of capsules from pharmacies, and changed the code for capsules in the national drug database to "obsolete."[48] After the generics developed equivalents for the reformulated tablets, Abbott again transitioned to a new (marginally lower-strength) tablet, stopped selling the original tablets, and again changed the database code to "obsolete."[49] In removing the old drugs from the market, Abbott engaged in what has since been deemed a "hard switch."

Because of the "nature of the pharmaceutical drug market," the court applied the Rule of Reason.[50] The defendants' proposed standard of per se legality "presuppose[d] an open market where the merits of any new product [could] be tested by unfettered consumer choice."[51] But in this case, defendants "allegedly prevented such a choice by removing the old formulations from the market while introducing new formulations," thereby justifying "an inquiry into the effect of [d]efendants' formulation changes."[52]

The court did not require plaintiffs "to prove that the new formulations were absolutely no better than the prior version or that the only purpose of the innovation was to eliminate the complementary product of a rival."[53] Rather, "if [p]laintiffs show anticompetitive harm from the formulation changes, that harm will be weighed against any benefits presented by [d]efendants."[54]

41 *Id.*
42 *Id.* ¶ 1011.
43 *Id.* ¶ 1031.
44 *Id.* ¶ 1025.
45 *Id.* ¶ 1028.
46 *Id.*
47 432 F. Supp. 2d 408 (D. Del. 2006).
48 *Id.* at 415–16.
49 *Id.* at 418.
50 *Id.* at 422.
51 *Id.*
52 *Id.*
53 *Id.*
54 *Id.*

The court also found it irrelevant that the reformulation did not completely bar the generics from entering the market, but only prevented automatic substitution at the pharmacy counter. The analysis asks not whether exclusionary conduct bars competitors "from all means of distribution," but whether it precludes access to the "cost-efficient ones."[55] While generics "may be able to market their own branded versions of the old TriCor formulations, they cannot provide generic substitutes for the current TriCor formulation, which is alleged to be their cost-efficient means of competing in the pharmaceutical drug market."[56] Such an opportunity "has allegedly been prevented entirely by [d]efendants' allegedly manipulative and unjustifiable formulation changes," and "[s]uch a restriction on competition, if proven, is sufficient to support an antitrust claim."[57]

In short, in the first judicial treatment of product hopping in the U.S., the court offered a thoughtful approach that considered the realities of pharmaceutical markets, in particular the importance of generic substitution, and relied on the Rule of Reason in balancing the anticompetitive and procompetitive effects of product hopping. Later courts, however, limited the reach of the ruling by cabining it to the "hard switch" scenario.

Walgreen: Soft Switch, Simplistic Choice

In particular, such a course was shaped by the second case, *Walgreen v. AstraZeneca Pharmaceuticals*, which involved AstraZeneca's conversion from heartburn drug Prilosec to Nexium.[58] The plaintiffs alleged that there was "almost no difference" between the drugs and there was "no pharmacodynamic reason" the two forms would have different effects in the body.[59] The plaintiffs also alleged that AstraZeneca aggressively promoted and detailed Nexium to doctors while stopping its promotion and detailing of Prilosec.[60] And they claimed that AstraZeneca was able to switch the market (to a drug receiving patent protection for an additional 13 years) only through "distortion and misdirection in marketing, promoting, and detailing Nexium."[61]

Unlike the court in *Tricor*, the District of Columbia court ignored the plaintiffs' detailed allegations of the "price disconnect" in pharmaceutical markets (by which the doctor who prescribes the product does not pay for it, and the consumer (or her insurer) who pays for it does not choose it). The court granted AstraZeneca's motion to dismiss, concluding that "there is no allegation that AstraZeneca eliminated any consumer choices."[62] But that conclusion rested on three factual assertions, all of which required the court to ignore the price disconnect. The court asserted as facts that:

- AstraZeneca "added choices"[63] by "introduc[ing] a new drug to compete with already-established drugs"[64];
- Determinations of "which product among several [are] superior" are "left to the marketplace"[65]; and
- "New products are not capable of affecting competitors' market share unless consumers prefer the new product."[66]

Each of those factual assertions contradicted plaintiffs' allegations of the price disconnect and its effects. In a price-disconnected market, switching doctors' prescriptions from one branded product to another does not "add choices," but effectively denies consumers the choice of obtaining a generic of the original rather than the reformulated brand product. Moreover, the question is not "which product among several is superior," but rather which product offers the consumer the best trade-off between price and quality, a determination that "the marketplace" cannot make in a price-disconnected market. In fact, the switching of the market from the original to the reformulated version certainly is capable of affecting competitors' market shares despite consumers' preferences. The court's contrary assertion ignored not only the plaintiffs' detailed allegations, but also the economic rationale of 50 state DPS statutes and the Hatch-Waxman Act.[67] None of those statutes would be necessary if consumers in fact revealed their preferences through price/quality choices.

In addressing a soft switch, the court confronted a different scenario than that in *TriCor*. But the divide between hard and soft switches did not need to be as stark as the court made it. The die was cast, however, when the court articulated a version of consumer choice that, even if it makes sense in non-pharmaceutical markets where consumers make the price/quality tradeoff, does not capture the realities of drug markets.

55 *Id.*
56 *Id.*
57 *Id.*
58 53 F. Supp. 2d 146 (D.D.C. 2008).
59 *Id.* at 149.
60 *Id.*
61 *Id.* at 148–49.
62 *Id.* at 151.
63 *Id.*
64 *Id.*
65 *Id.*
66 *Id.*
67 *Id.*

Suboxone: Hard/Soft Switches, Nuanced Analysis

The third court considered elements of both hard and soft switches in a nuanced analysis of the regulatory regime. In *In re Suboxone Antitrust Litigation*,[68] the Eastern District of Pennsylvania court considered allegations that Reckitt switched the market from opioid-dependence-treating Suboxone tablets to sublingual film. Reckitt allegedly promoted Suboxone film to physicians, disparaged Suboxone tablets, warned of false safety concerns, publicly announced the removal of tablets for these fabricated safety reasons but did not remove the tablets until six months later, and raised the price of tablets in relation to film even though film was more expensive to manufacture and package.[69]

The court began its analysis by noting that "[b]ecause ordinarily innovation will also inflict harm upon competitors, 'courts should not condemn a product change . . . unless they are relatively confident that the conduct in question is anticompetitive.'"[70] But "when the introduction of a new product by a monopolist prevents consumer choice, greater scrutiny is appropriate," with the test (similar to *TriCor*) for whether conduct is exclusionary based "not [on] total foreclosure, but whether the challenged practices bar a substantial number of rivals or severely restrict the market's ambit."[71]

The court found that the conduct at issue "seems to fall somewhere between that alleged in *Walgreen* and *TriCor*."[72] The behavior was more concerning than that in *Walgreen* because Reckitt removed tablets from the market, but less concerning than that in *TriCor* because Reckitt did not buy back tablets or label an old product "obsolete."[73] The court made clear that "simply introducing a new product on the market, whether it is a superior product or not, does not, by itself constitute exclusionary conduct."[74] Rather, "[t]he key question is whether the defendant combined the introduction of a new product with some other wrongful conduct, such that the comprehensive effect is likely to stymie competition, prevent consumer choice and reduce the market's ambit."[75] Crucially, "[t]his analysis must be undertaken with the somewhat unique characteristics of the pharmaceutical market in mind."[76]

Applying this analysis, the court found that "the facts presented sufficiently allege that the disparagement of Suboxone tablets took place alongside 'coercive' measures" as "[t]he threatened removal of the tablets from the market in conjunction with the alleged fabricated safety concerns could plausibly coerce patients and doctors to switch from tablet to film."[77] The court recognized that "[p]laintiffs have plausibly alleged that various market forces unique to the pharmaceutical industry make generic substitution the cost-efficient means of competing for companies selling generic pharmaceuticals."[78] In particular, the court noted that the "disconnect" that "exists between the person paying for the prescription and the person selecting the appropriate treatment" led to "the ordinary market forces that would allow consumers to consider price when selecting a product [being] derailed."[79] A patient would not be able to "simply request to receive a generic from his or her pharmacist because the film and the generic tablets are not [bioequivalent] and thus may not be substituted."[80] Although the court noted the dichotomy between hard and soft switches, it conducted an analysis rooted in the regulatory framework, ultimately concluding that the plaintiffs "plausibly pleaded exclusionary conduct."[81]

Doryx: Ignored Regulatory Regime

While the *Suboxone* court grounded its decision in the regulatory framework, the Third Circuit in *Mylan Pharmaceuticals v. Warner Chilcott* (*Doryx*)[82] did not. In that case, Warner Chilcott engaged in an array of behaviors that resembled those of Abbott in *TriCor I*: it stopped selling capsule versions of acne-treating Doryx to wholesalers; removed Doryx capsules from its website; worked with retailers to "auto-reference" the Doryx tablet whenever a doctor filed a Doryx prescription; informed wholesalers, retailers, and dealers that "Doryx Capsules have been replaced by Doryx Tablets;" and bought back and destroyed capsule inventory.[83] Despite allegations of hard switches and lack of economic sense, the court rejected Mylan's claims of anticompetitive

68 64 F. Supp. 3d 665 (E.D. Pa. 2014).
69 *Id.* at 674.
70 *Id.* at 679–80.
71 *Id.* at 680.
72 *Id.* at 681.
73 *Id.*
74 *Id.* at 682.
75 *Id.*
76 *Id.*
77 *Id.*
78 *Id.* at 683–84.
79 *Id.* at 684.
80 *Id.*
81 *Id.*
82 2016 WL 5403626 (3d Cir. Sept. 28, 2016).
83 *Id.* at *3.

conduct, finding that "Mylan was not foreclosed from the market."[84] Even though it found, "viewing the facts in the light most favorable to Mylan, that Defendants had indeed made the Doryx 'hops' primarily to 'delay generic market entry,'" it affirmed summary judgment for the Defendants.[85]

After concluding that the plaintiff – the competitor generic manufacturer – failed to adduce evidence of monopoly power, the court indicated that it would have affirmed summary judgment on the alternative ground that the plaintiff failed to satisfy its initial burden of introducing evidence of anticompetitive conduct under the rule of reason.[86] But the court never explained what it considered to be an anticompetitive effect; nor did it consider whether a substantial reduction in the prescription base available for automatic generic substitution would count. Instead, in direct opposition to the Supreme Court's instruction that the relevant effect is on consumers, not competitors,[87] the court focused exclusively on the effect of Warner's conduct on Mylan, the generic *competitor,* never even mentioning the effect on *consumers*.[88]

Regarding the product hops' effects on Mylan (and assuming this were an appropriate inquiry, which it is not), the court offered only a series of non-sequiturs, asserting that Warner's conduct was not anticompetitive because:

- Mylan received a 180-day exclusivity period under the Hatch-Waxman Act (although Mylan's sales at relatively high generic prices is irrelevant to whether Warner substantially reduced the number of sales and profits that Mylan would have made absent the product hops);
- Mylan set its generic price higher than the brand price for a period of time (although the Court failed to explain the relevance of this fact and did not consider whether the product hop caused Mylan's pricing strategy — a generic unable to distribute its product through automatic substitution might well increase price for the sales it can make);
- Mylan made profits of $146.9 million on the sales of generic Doryx (although that number is meaningless unless compared to the profits that Mylan would have made absent the product hops).

Finally, the Court offered a hodge-podge potpourri for courts to decide other product-hopping cases, stating that courts should balance exceedingly broad policy goals, such as "encouraging innovation," "protect[ing] consumers," and "ensur[ing] fair competition."[89] Among the "non-exhaustive" factors that courts may consider is the need to be "wary" of "turning courts into tribunals over innovation sufficiency."[90] Presumably another factor to consider is the decisions of 50 states and Congress to promote generic competition. The court provided no guidance at all on how courts are to balance these objectives.

Namenda: Robust Regulatory Analysis, Improper Coercion Focus

The final decision was offered by the Second Circuit. In *New York v. Actavis PLC (Namenda)*, the court upheld a preliminary injunction preventing brand firm Forest from withdrawing its original drug from the market.[91] As Forest's Alzheimer's drug Namenda IR (taken twice a day) neared the end of its patent term, it introduced Namenda XR (taken once a day), with a patent expiring 14 years later. Although it initially planned to keep IR on the market (the soft switch), it later implemented a plan to effectively withdraw IR from the market (the hard switch).

The court found that "neither product withdrawal nor product improvement alone is anticompetitive" but "when a monopolist *combines* product withdrawal with some other conduct, the overall effect of which is to coerce consumers rather than persuade them on the merits . . . and to impede competition . . . its actions are anticompetitive under the Sherman Act."[92] The court also rejected a defense based on "free riding" since "generic substitution by pharmacists following the end of Namenda IR's exclusivity period . . . is authorized by law; is the explicit goal of state substitution laws; and furthers the goals of the Hatch–Waxman Act by promoting drug competition . . . and [] preventing the 'practical extension

84 *Id.* at *10.
85 *Id.* at *5.
86 *Id.*
87 *E.g.*, Harrison Aire, Inc. v. Aerostar Int'l, Inc., 423 F.3d 374, 385 (3d Cir. 2005) (noting that Supreme Court in *Brunswick Corp. v. Pueblo Bowl-O-Mat, Inc.*, 429 U.S. 477 (1977) held that "antitrust laws protect consumers, not competitors").
88 *Mylan*, 2016 WL 5403626, at *11.
89 *Id.* at *12.
90 *Id.*
91 787 F.3d 638 (2d Cir. 2015).
92 *Id.* at 653–54.

of [the brand firm's] monopoly . . . beyond the expiration of the patent.'"[93]

The court held that defendants' justifications were pretextual, and that even if they were not, any benefits "are outweighed by the anticompetitive harms."[94] It found monopolization from the combination of "withdrawing a successful drug from the market" and "introducing a reformulated version of that drug," which forced patients to "switch to the new version" and "imped[ed] generic competition, without a legitimate business justification."[95] The court then upheld an injunction because of the irreparable harm from the "planned hard switch strategy,"[96] requiring defendants to make Namenda IR tablets available.[97]

While the court understood the regulatory framework, it applied a test based on coercion that was underinclusive in targeting antitrust harm. The court stated that "[a]s long as [d]efendants sought to persuade patients and their doctors to switch from Namenda IR to Namenda XR while both were on the market (the soft switch) and with generic IR drugs on the horizon, patients and doctors could evaluate the products and their generics on the merits in furtherance of competitive objectives."[98] The court focused on Forest's "forc[ing] patients to switch" from Namenda IR to Namenda XR, and cited defendants' figures that a soft switch would convert only 30% of patients while a hard switch would convert 80% to 100%.[99] The court stated that "[h]ad [d]efendants allowed Namenda IR to remain available until generic entry, doctors and Alzheimer's patients could have decided whether the benefits of switching to once-daily Namenda XR would outweigh the benefits of adhering to twice-daily therapy using less-expensive generic IR (or perhaps lower-priced Namenda IR)," but "[b]y removing Namenda IR from the market prior to generic IR entry, [d]efendants sought to deprive consumers of that choice."[100]

While the court appreciated the regulatory regime, its coercion-based framework does not make room for potential harms from a soft switch that arise from the unique nature of drug markets and that could involve profit sacrifice.

CONCLUSION

Product hopping is nuanced behavior that implicates antitrust law, patent law, the Hatch-Waxman Act, and state drug product selection laws. This article has shown the complexity of the behavior and courts' varied treatment of it.

93 *Id.* at 657–58.
94 *Id.* at 655.
95 *Id.*
96 *Id.* at 660–61.
97 *Id.* at 649–50.
98 *Id.* at 654.
99 *Id.*
100 *Id.* at 655.

IP Management

Analysing Patent Terms and Citations to Determine the Value of Gene Therapies

Peter van Dongen
is a researcher and engineer at the Research and Promotion department of the Netherlands Patent Office

Zainab Noor El Hejazi
is a graduate student in the Health and Life Sciences at the Free (VU) University Amsterdam, The Netherlands

Eric Claassen
is a professor at the Free (VU) University Amsterdam, Athena Institute for Innovation and Communication in the Life sciences, The Netherlands

ABSTRACT

Gene therapies hold great promise for treatment of diseases but so far their market authorisation has been limited. This paper describes the development of patented gene therapies in the sector of life sciences and health. It was found that the annual number of patented gene therapies increased significantly till the year 2005. A cluster analysis of gene therapies patented in 1995 shows that: a) more than eighty percent has been renewed for more than fifteen years (fifty three per cent till the maximum patent term) and b) fifty per cent of the patents have been licensed. There is a statistically significant correlation between the numbers of citations in future patent applications by third parties and the number of years of patent renewals. A case study of the patent EP 0833934 of biotechnology start- up Crucell demonstrates that the number of citations by third companies to this patent even predicts the companies' market capitalization. This research yielded evidence that the number of patent citations can be used as indicator to determine the value of gene therapies. Such information is of relevance for both the patentee and investors.

Journal of Commercial Biotechnology (2017) 23(2), 61–73. doi: 10.5912/jcb777

Keywords: Biotechnology, gene therapies, patents, citations, value, market capitalization

INTRODUCTION

In the sector of the life sciences and health numerous biotechnology inventions have contributed to significant improvements in plant breeding, food supply, manufacturing of drugs and health care. In this paper modern biotechnology is defined as an array of technologies that uses recombinant DNA (rDNA) in biological systems for practical means[1]. Biotechnology can enable gene therapy by the delivery of nucleic acid polymers into patients' cells as a drug to treat a disease or as medical preparations containing genetic natural material inserted into cells to treat genetic diseases in persons. Bearing in mind that some four per cent of human mankind has genetic disorders[2] gene therapies hold great promise for medical use. Their practice has been a topic of much ethical debate in society since the 1990's which was aggravated by the death of eighteen year old Jesse Gelsinger at the university of Pennsylvania in 1999[3].

Nowadays, the European Medicines Agency receives less than five applications[4] for gene therapy medical products (http://www.ema.europa.eu/GTMP) per year and so far only Glybera® and Strimvelis® have received market authorisation. On the other hand, the outlook and consequences of patenting DNA and genes for therapies and research are well documented[5–7] and the number of gene patents[8] was on the rise. With the wake of biotechnology companies (e.g. Genentech, Amgen, Chiron) discussions about ownership of knowledge

Correspondence:
Peter Van Dongen, Netherlands Patent Office, Netherlands. Email: peter.vandongen@rvo.nl

funded by governmental financial research organisations (e.g. National Institutes of Health (NIH) started. The role and implications of intellectual property rights (IPR) for innovations and the development of the biotechnology sector became apparent[9]. Since the eighties the potential cures for patients with genetic malfunctioning organs, numerous technologies have been patented in domains like cancer, immunology and vaccines. In this sector in particular the commercialisation of academic patents both in the USA and the EU is evident[10, 11]. On a global scale both pharma and biotechnology companies that manage their IPR well can become very successful[12, 13].

CAN PATENTS ALSO HOLD VALUE FOR GENE THERAPIES?

The number of company patent applications or patents in a particular sector can be associated to R&D expenditures and innovativeness[14]. But apparently for promising new gene therapies there is an interesting but contrasting situation where numerous companies file large numbers of patent applications while their commercial viability is still unproven? Companies usually file and renew their product and process patents only in those countries where they expect that customers will use their appropriated inventions and healthy gross margins on products sold or licensees are expected and realised. In the past decades several researchers used patent citations to study the relations between the financial value of patents, sales and the market value of the patent owner in various sectors of the economy but not for gene therapies in the life sciences and health sector. The financial value of a patent is often defined as the net margin between the sum of revenues of sold volume of patented protected products during its' patent term (incl. license revenues minus the costs to file and renew the patent[15]. The patent family size and opposition may also be used as indicators to determine the value of patents[16, 17]. Following the patent renewal fees paid for 964 inventions filed in the USA and Germany both researchers concluded that patents, renewed to the full term, were significantly higher cited. They conclude that 'patents reported to be relatively valuable by the companies holding them are more heavily cited in subsequent patents'. Studying some 4 900 R&D projects in the pharma sector a 'one per cent increase of number of citations corresponding with 0, 3 per cent increase in total sales' was found[18]. When combining data of market values of 4 864 publically traded companies in the USA and all granted US patents between 1963 and 1999 for technologies of these companies in a broad range of sectors of economy, it became evident that patent citations can provide a useful means to indicate the market value of a company[19]. These researchers conclude that 'an extra citation per patent boasts the market value by 3 per cent' and 'self-citations appear to be more valuable than external citations by third parties'. Since market values of companies in the US and the EU can be related to the numbers of citations to their patents[20, 21] investors are interested in companies with patents that receive a lot of citations. Due to cultural differences and the fact that there are only few large biotechnology companies in Japan patents are less important than secrecy agreements[22].

OBJECTIVES OF THIS RESEARCH

To our knowledge most research on the value of patents has been limited to the automotive, chemistry, electronics, and pharma sectors[23, 24] excluding biotechnology. In one specific field of computer tomography scanners technology an empirical analysis showed effects of close relations between patent citations and increase in product margins[25]. Given the situation in the health sector in general and the gene therapies in particular following research questions are addressed: a) Can indicators be identified that might explain why the patent term of gene therapy patents have been extended for the full length of 20 years, b) Can the origin of gene therapies and important inventors be identified and c) Can the value of patented gene therapies be related to the identified indicators? As a specific objective in this research an effort will be made to identify those indicators that can determine the value of a start- up that exploits patented gene therapies.

Under the assumption that the value of a gene therapy patent for a company is positively correlated to its' patent term four hypotheses will be tested:

1. The value of a gene therapy patent is positively to the number of designated countries in the patent application
2. Idem, to number of product / process claims in the patent application
3. Idem, to the number of licenses for the patent
4. Idem, to the number of citations (in future patent applications) to the patent

METHODOLOGY

A global patent analysis of the life sciences and health sector between 1995 and 2005 will be carried out to identify and quantify the numbers of patent applications. Within that sector all patent applications in the domains of cancer, cardio vascular diseases, medical imaging,

immunology, vaccine development and neurodegenerative disorders have been identified. For this analysis the Patstat database and the international patent classification codes for these domains will be used (**Appendix 1**, http://www.epo.org/searching). Based upon the results of this analysis the global patent landscape of the most important companies in this sector can be quantified. This landscape (**Appendix 2**) will be used as a starting point for a patent cluster analysis measuring the performance of the patentees of gene therapies as of 1995.

To provide support for the hypotheses, a quantitative, longitudinal analysis of patented gene therapies of companies and research institutes has been carried out. A time frame between 1995 and 2015 was applied to collect data on the patent application routes, patent terms, number of designated countries (or patent family size), number of patent claims, citations and licenses. These data were then used in a patent cluster analysis to identify all patent applications that have been filed in the same year (1995) and within exactly the same patent classification classes A61K48, C12N7 and C12N15/86. In these patent classes the gene therapy of the Dutch start- up company IntroGene/ Crucell was patent i.c. EP 0833934 '*Packaging systems of human recombinant adenoviruses to be used for gene therapy*'. Their patented PER.C6 technology has been selected since the exploitation of this patent is well known. It has been exploited and managed for the full patent term of 20 years even after the acquisition of the company by Johnson and Johnson in the year 2011. So this patent of Crucell[26] has been selected as a benchmark for our research and cluster analysis since it has been successfully managed for several exclusive applications in niche markets (e.g. by licenses to companies like Transgene, DSM, Genzyme and research organisations as the NIH). The PER.C6 technology was used as a platform technology for the development of vaccines and for future use in immunology.

Using the same patent classification codes as EP 0833934 and the database EPODOC similar gene therapy patents which were filed in 1995 could be identified as well as their applicants. These databases, used by patent examiners at the European Patent Office, also contain bibliographic information and citations to patents and patent applications in over 90 countries[27]. During the examination process, examiners at a patent office have to identify prior disclosures of a technology describing the claims in the patent application in full or partially, thus revealing documents as the closest state of the art in their search reports. If such documents are found they are submitted to the applicant of the new patent application and will be cited in future applications for inventions in the same technical domain[19]. The number of times that a particular patent publication is cited in future patent applications may then be a used as an indicator of its' technical significance.

Once the indicators have been identified that explain why patent holders of gene therapies renew their patent terms till the maximum patent term of twenty years the research will continue and study if these indicators can be linked the market value of the company, using different methods for patent valuation[28] and the theories for the diffusion of medical innovations[29, 30] . In 2014 and 2015 interviews with stake holders in the Dutch life sciences sector were held to validate and confirm the findings of our quantitative findings. Their opinions about the importance of strategic IPR management for biotechnology companies, business development and market development of new products were listed. Subsequent interviews with the original inventors of the PER.C6 technology, the IP managers of Crucell, V/C's that provide financial resources and stock holders enabled more insight into what happened after the discovery and the global exploitation of this patented gene therapy.

RESULTS

Figures 1a and 1b show the developments of the numbers of annual gene therapy patent applications and the patent applications in six domains of the life sciences and health that have been filed between 1985 and 2013. These patent applications include all patent documents that describe worldwide filed (WO/ PCT) patent applications and European filed (EP) applications in the domains like cancer (36,375), cardiovascular diseases (3,261), medical imaging (1,557), immunology (17,348), vaccines development against infectious diseases (13,065) and neurodegenerative disorders (5,859). For gene therapies patent applications an increase till the year 2003 (and a decrease of 64 per cent since) can be observed. In the domains of

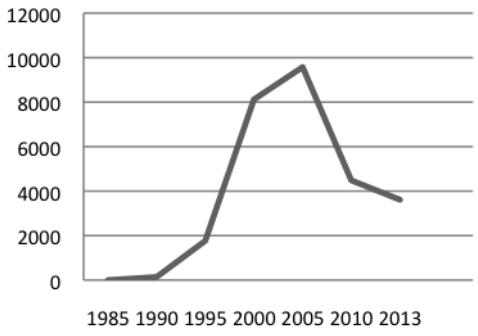


Figure 1a: Gene therapy WO and EP patent applications per year (*)
(*) Significant at p= 0,01

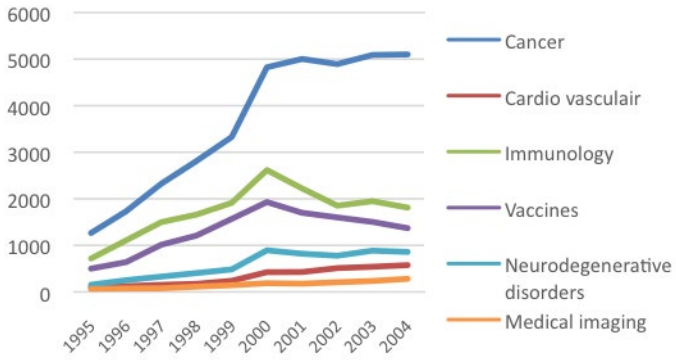


Figure 1b: Life science patent applications (N= 77, 435)

cancer, neurodegenerative disorders, cardiovascular diseases and medical imaging the number of applications increases till 2005, but a reduction of applications for immunology (twenty two per cent since 2000) and vaccines (thirty three per cent since 2000) took place.

Using the Thomsom Scientific WPI Index the identified patent applications can be converted into the domains of use (Appendix 2). Within the scope of this research there is a focus on gene therapies related to patent applications in the domains of cancer, immunology and vaccines only. It is clear that most gene therapy patent applications have been filed by companies and universities headquartered in the USA, followed by Germany, Japan, United Kingdom, France, Canada, Switzerland, The Netherlands, Sweden and Korea. GlaxoSmithKline, Merck and Bayer were the companies that filed most applications followed by a number of biotechnology companies and universities. Especially in the domain of vaccine development high percentages of technologies using genetically modified organisms are found. Between 1995 and 2005 on average only 1, 8 per cent of the patents in the domains of cancer, immunology and vaccine development are gene therapy related. Based upon this percentage and the total numbers of patent applications in these domains an average of some 120 unique gene therapy inventions is expected to be patented per year. Figure 1a shows an annual number of 1, 768 of WO and EP patent applications in 1995 which means that some 120 unique gene therapy inventions have become registered in some 15 countries (= 1, 768 / 120).

The methodology yielded a worldwide patent cluster of ninety three gene therapies similar to EP 0833934 of Introgene/ Crucell that were also patented in the year 1995. Further analysis enabled the identification of the applicants and the quantification of data on their patent terms, granting procedures (including opposition), number of claims, countries of designation, number of licenses and citations by third parties (Appendix 3, table A). Seventy six of these patents have been granted to companies or universities. Additionally, seventeen patent applications have not been granted for several reasons. Thirty eight gene therapy patents of the seventy six granted gene patents have been licensed to third parties to e.g. Oxford Biomedica Ltd. (eleven gene therapy patents from Chiron - Viagene Inc.) and the National Institutes of Health in the USA (five gene patents from US universities and three from companies). H. Gruber and D. Jolly, both employed by Chiron- Viagene Inc., have been the most important inventors in gene therapy patent applications. The statistical analysis of the patent cluster in **table 1** reveals that fifty three per cent of the patents have been granted and renewed till the maximum patent term of twenty years. Additionally twenty eight per cent have been renewed for more than fifteen years. So in total more than eighty per cent of gene therapy patents were renewed for more than fifteen years. Apparently, patentees of gene therapies in 1995 renewed their patents for more years when their patent is: a) granted in the USA, b) licensed to third parties and c) have been cited more frequently. Plotting the patent terms (in years of validity) of the granted patents against the actual numbers of patents granted (indicator A), their percentage of licenses (indicator D) and the number of citations (indicator E) significant differences are observed. So based upon these results only hypotheses three and four will therefore be accepted.

Next to the significant differences in renewals for patents filed with a priority in the USA, most of the patent holders also decided to maintain their patent in the UK, France, Germany and Japan. No significant differences were found for patents that had a priority filing in other countries than the USA and were subsequently renewed by their patent holders for the different sets of time frames as indicated. Most of the gene patent applications have been filed by companies and universities headquartered in the USA followed by French organisations (Appendix 3, figure A). Some companies choose to file their priority patent applications in 1995 not at the US Patent and

Table 1: Indicators of significance (*) that determine the patent term of gene therapies

Patent terms (in years)	20	15 – 19	10- 14	< 10
Indicators (A, B, C, D and E)				
A. Number of granted patents (N=76)	40	21	12	3
US priority (60) (*)	32	18 (*)	10 (**)	0 (**)
French priority (9)	3	2	1	3
UK priority (2)	0	1	1	0
EP priority (2)	2	0	0	0
Denmark priority (1)	1	0	0	0
German priority (1)	1	0	0	0
Israëli priority (1)	1	0	0	0
B. Avg. number of countries	35	30	42	33
C. Avg. number of claims	31	21	18	24
Patents with product claims	36	2	0	0
Patents with process claims	35	15	7	4
D. Number of license agreements (*)	21	11 (**)	5 (**)	0 (**)
E. Avg. number of citations (*)	53	41 (*)	21 (**)	6 (**)

Significant at (*) p= 0, 05 and (**) p= 0, 01, R^2 (patent terms – license agreements) = 0, 96 and R^2 (patent term – average number of citations) = 0, 99

Table 2: Comparison of numbers of (self-) citations in future patent applications to patents filed in 1995 with three reference patents

Company	Patent	Number of citations (A)	Number of self-citations (B)	Name
Patents filed in 1995				
IntroGene/ Crucell	US6033908	206	69	PER.C6®
Transgene	US6040174	269	29	
Reference patents				
Stanford/ Boyer	US4237224	401	58	rDNA process
Idem	US4468464	124	9	rDNA product
Cetus/ Mullis	US4863202	6578	11	PCR®

Trademark Office (USPTO) but at national offices or at the European Patent Office (EPO) as Introgene/ Crucell did for their EP 0833934 patent application. Analysing the life cycles of US patent applications a granting percentage of eighty six per cent at the USPTO and a rate of granting an US patent application of less than four years can be observed. So patentees at the USPTO can expect a fast and efficient patent granting procedure. However, the practice at the USPTO differed considerably from the practice at the European Patent Office. There a granting percentage of less than seventy per cent can be observed while granting procedures took more than ten years on average (Appendix 3, table B). E.g. the EP 0833934 patent application from Introgene/ Crucell was filed in 1995 and granted in 2004. Thirteen companies and two universities withdrew their patent applications within (five to seven) years after the filing date of their applications and two patent applications have been revoked. Two patent applications of the total of seventy six granted gene technology patents faced opposition after grant at the EPO.

The number of citations of the Introgene/ Crucell patent EP 0833934 (equivalent to US patent US6033908) in future patent applications is relatively high. The analogy between citations to scientific papers and patent citations can be taken as point of reference. Where papers about breakthrough scientific discoveries will be cited in future scientific papers by peer researchers, the concordant inventions might be patented. It seems only logical that over time important patented inventions will have a higher chance to be cited by future patent applicants. Besides, looking at the data in table 2 the idea that the proportion of self- citations to all citations to the patent of a start- up company could be used as an indicator to determine the patent value and the acceptance of a gene therapy becomes apparent. In order to provide evidence for this idea the number of self-citations as percentage

of the total number of citations in three particular gene therapy patents was compared with data from famous global patented innovations.

The priority patent of Introgene / Crucell (figure 2a) has also been cited by its' spin- off company Galapagos in 1999 while in 2009 and 2010 the number of both self-citations and citations by third parties reached a higher level again. Following the history of citations of the famous rDNA process patent US4237224 of Boyer and Cohen of Stanford/ Genentech (figure 2b) it can be observed that after the filing date of this patent the company applied for future patents citing this first patent, as well as third parties did. During the mid- nineties and still after the lapse of the patent it is cited in patent applications by third parties. From figures 2a and 2b it is evident that there is a need for the introduction of a time correction factor, thereby reducing the importance of self- citations to the priority patents of a start-up company.

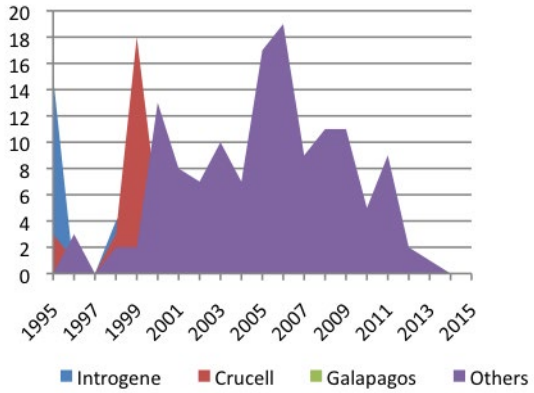


Figure 2a: Number of citations to the US6033908 of Crucell in other patent applications per year

Some researchers [17] describe the relation between the numbers of all patent citations and the market value of companies in an equation as: ln citations = 0,314 ln market value + 2. However, a direct relation between the (market) value of a biotechnology start- up company and the number of citations to their important (priority) patents has not been developed previously. For start-up Crucell the relations between the parameter of the natural logarithm of the total number of citations (= sum of the citations by third parties and self-citations in future patent applications) on the one hand side and the parameters of stock value development and market capitalization on the other hand side, were analysed. The relations between these parameters show an interesting correlation over time. The accuracy of these correlations improves if only the total number of citations by third parties is used. The correlations become even better once a time correction factor of 1, 12 is implemented. Figure 3 shows that the number of citations by third parties in a particular year even predicts the market capitalization of the start- up in the following year.

The established biotechnology company Chiron-Viagene Inc. was the largest applicant of gene therapy patents in 1995 (Appendix 3, table A). For the domains of cancer, immunology and vaccines the numbers of patent applications by Chiron- Viagene Inc. and biotechnology start- up company Introgene/ Crucell filed between 1995 and 2005 are presented in table 3. It is obvious that the start- up Crucell might be regarded as a serious competitor to Chiron- Viagene Inc. only in the domain of

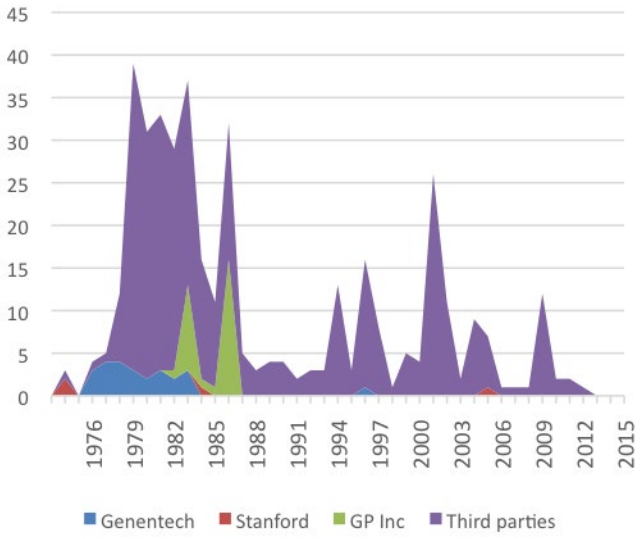


Figure 2b: Number of citations to US427224 of Genentech in other patent applications per year

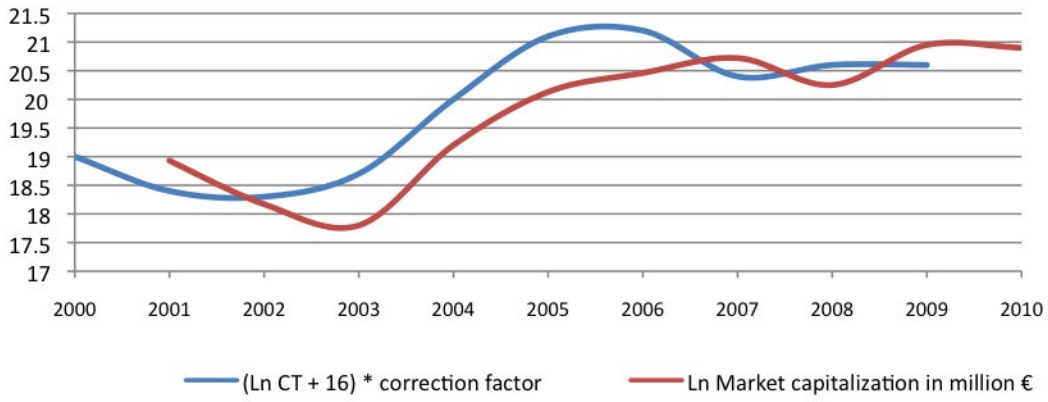


Figure 3: Time lag effect between 1, 12 * the number of citations by third parties to US6033908 (blue colour) and the market capitalization of Crucell (red colour) between 2000 and 2010

Table 3: Number of gene therapy patent applications per company filed between 1995 and 2005 in three domains (and worldwide ranking)

Domain	Cancer	Immunology	Vaccine
Company			
Chiron- Viagene Inc.	182 (27)	169 (9)	119 (10)
Introgene / Crucell	23 (-)	37 (76)	45 (39)

(N) = ranking on the global list of patent applicants

vaccines. But a comparative analysis of the patent applications by Introgene/ Crucell and Chiron- Viagene Inc. in 1995 demonstrates the different characteristics of their patent portfolio.

Figure 4 shows very clearly that the only patent of Introgene/ Crucell in their portfolio has been cited in 206 future patent applications while the twelve patents of Chiron- Viagene Inc. has been cited on average in sixteen future patent applications between 1995 and 2015. Other data show that the number of licenses of the patent of Introgene/ Crucell is ten times higher compared to average license percentage of the other seventy six granted patents for gene therapies in 1995. The priority patent application EP 0833934 (= US6033908) was filed on June 15, 1995 and subsequently a patent portfolio of forty eight nationally registered patents and ten US divisionals was built. In order to generate revenues the start-up company Introgene/ Crucell decided to license their patented PER.C6® human cell line technology, after having received FDA approval for market authorisation, to third parties and major patent holders in the other life sciences and health domains (Merck and co., Rhône Poulenc, Millennium Pharma, Aventis Pasteur and GlaxoSmithKline) which eventually also led to the acceptance and dissemination of their technology. In this highly competitive field it was of key importance to appropriate this core technology [31] and to cooperate with third parties.

The PER.C6® technology of Crucell contains a package of tools and know-how based on Crucell's priority patent EP0833934 (= US6033908). It provided a safe and cost-effective manufacturing system for high- yield, large-scale production of vaccines and monoclonal antibodies as shown in table 4. It is especially useful for vaccine manufacturing that requires the production of hard-to-grow viruses and holds the key to making such vaccines affordable on global scale. Johnson & Johnson acquired Crucell in 2011 and then delivered more than eighty five million doses of viral vaccines to UNICEF to protect people in over sixty countries against five serious childhood infections (diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenza type B).

LIMITATIONS

Gene therapies have been patented since 1985 and the scope of this research was to identify those indicators that determine the value of patented gene therapies. The methodology and a case study of the biotechnology start-up company Crucell enabled the identification and analysis of a patent cluster of similar gene therapies. The size of the studied patent cluster was ninety three gene patent applications filed in 1995.

CONCLUSIONS AND DISCUSSION

This research shows that:

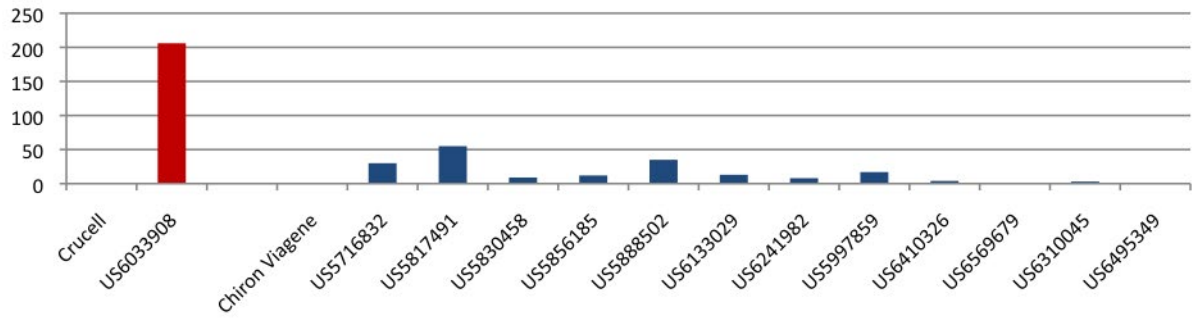


Figure 4: Comparison of the number of citations of one patent from Crucell and twelve patents from Chiron-Viagene Inc. between 1995 and 2015

Table 4: Vaccines based upon the patented PER.C6 technology of Crucell

Quinvaxem®	Fully liquid vaccine for protection against five major childhood infectious threats
Hepavax-Gene®	Recombinant hepatitis B vaccine
Hepavax-Gene® TF	
Epaxal®	Aluminum- free hepatitis A vaccine
Dukoral®	Oral vaccine against cholera

A.
The number of gene therapy patent applications increased significantly between 1985 and 2005 and decreased since.
B.
In a cluster of patented gene therapies similar to EP 0833934 (of biotechnology start- up Introgene/ Crucell) ninety three gene therapies were filed in 1995 and granted and registered in some forty countries. The statistical analysis of this patent cluster provide evidence that: a) a US patent priority filing, b) the number of patent license agreements and c) the number of citations *by third parties* is significantly correlated with the length of the patent term.
C.
In the case of the biotechnology start- up Crucell a close correlation was observed between the number of patent citations by third parties and the market capitalization of the company. Applying a time correction factor to the number of third party citations predicts this market capitalization even more accurately because of the acceptance of the use of the patented gene therapy over time.

Policy makers in the European Union, Japan and the USA have realised that the so- called red biotechnology in the sector of life sciences and health plays a crucial role in the development of the future public health. The increasing importance of the commercialisation of academic patents in this sector both in the USA and the EU is evident[31]. To this end the European Biotechnology Directive EG/ 98/44, revisions on IPR ownership in the national patent acts and TT policies at universities have an important contribution role[32]. Both legislation on the patentability of biotechnology subject matter and long term road maps on biotechnology research and funding will enable the contribution of scientific research to the growth of the sector of biotechnology. In many countries special biotechnology clusters (or regions) received substantial support at national/ regional level both in terms of financial assistance as well as in facility support[33]. The successful case of Introgene/ Crucell is special since at the time of the discovery and patenting of the invention of PER.C6 neither the Leiden university in The Netherlands nor its' faculty of science had a formal IP or TT policy in place. While the research was contracted by Introgene to the university and the inventors Frits Fallaux and Rob Hoeben were employed by the university the other inventors Bram Bout and Dinko Valerio were employees of Introgene. Between themselves they decided that the priority patent was filed in 1995 in the names of both the university and Introgene and later re- assigned and transferred to Introgene in 1997[34]. Nowadays, with established IP policies at university TTOs in place the power of attorney and permission by the Board of Directors of the university is usually required for such assignment of patents, which could delay both participation in contract research and/ or the formation of a start- up company based upon academic patents.

Where the adaptation of innovations often go hand in hand with early adapters in their networks and systems of communication[30], health innovations related to the treatment of diseases and disorders are subject to clinical trials and market authorization procedures by the Food and Drug Administration (FDA fda.gov) and the European Medicine Agency (ema.europa.eu). Once a biotechnology company went for an IPO and becomes stock listed, it will distribute news releases to the press and general public showing that their prospected

products have passed some of these trials, thus making their investors aware that these products have come closer to market entrance[34]. The use and acceptance of new medical innovations require time and perseverance. And 'although viral vectors may have become the vehicles for the gene therapist, more breakthrough inventions and technologies will be needed which will be based upon fundamental research'[35]. It is evident that the rate of acceptance also depends on the IP universities and companies. This is clearly demonstrated that in a comparison between an IP strategy favouring a non- exclusively licensed patented research tool (e.g. the UCLA for the rDNA process to research institutes and companies) at low costs and a IP licensing strategy of a production platform (e.g. Crucells' PER.C6® technology to companies) on an exclusive basis. Besides, it is known that the acceptation of a gene therapy and biotechnology by the general public also depends on perceptions of citizens to avoid risk[36].

Our research in the life sciences and health sector demonstrates that in the domains of cancer, neurodegenerative disorders, cardiovascular diseases and medical imaging the number of patent applications increased between 1995 till 2005. Next to the applicants from the USA and the EU both the absolute number of patent applications from China, New Zealand, India, Taiwan and Korea and their percentages increase. The number of patented gene therapies also increased till 2004 but the number of patents based on human genes is on the decline as off the year 1999[31]. Since 2010 most gene patents contains synthetic sequences[37]. Some 3,500 patents involving human genes will probably be invalidated in the USA after the decision of the US Supreme Court that isolated human genes are unpatentable[38]. Our research data contrast those findings which claim that the percentage of biotechnology patents and pharma patents show levels under their top levels of application of 1996[39]. On the other hand their data on important biotechnology applicants in 2005 and 2006 correspond with the names of the companies and universities that have been identified in this study (e.g. Genentech, Amgen, Chiron, Millennium Pharma, universities of California and Texas).

Based upon research on possible relations between patent citations (both self- citations and third party) and company market value in various sectors of the economy data have been collected which demonstrate a very skewed relations. Where some researchers[17] relate the numbers of all citations with the market value of companies the case of start-up company Crucell shows that only third party citations contribute to determine the market value. It has also been claimed that patent family size and opposition may be used as indicators to determine the value of patents[16]. However, in this research neither size nor opposition were found to be positively correlated to the patent term and renewals of patented gene therapies that have been filed by companies and universities in 1995.

The conclusions from this research are that the renewals of patented gene therapies are positive correlated to the number of licenses and number of patent citations, so that the patent term can be used as indicator to determine their value. In the case of the biotechnology start- up Crucell the number of citations by third parties to its' priority patent application EP0833934 in a certain year was positively correlated to its' market capitalization in the following year. The conclusion for this case is that the number of citations can be used to predict the company's value. This conclusion is not only relevant for the patent holder but also for investors and V/C's.

REFERENCES

1. Torrance, A.W. (2014) Gene concepts, gene talk and gene patents. *Miss. J. Of Science and Technology* (2010), 11(1): 157–191.
2. Alberts, B., Johnson, A., Lewis, J. Raff, M. Roberts, K. and Walter, P. (2012). Molecular Biology of the Cell, Garland Science, p.
3. Editorial (1999) *Nature* (401): 517–8.
4. Personal communication B. Leufkens, CBG MEB (2016).
5. Dutfield, G. (2006) DNA patenting: implications for public health research, *WHO bulletin*, 84(5): 388–392.
6. Jensen, K. and Murray, F. (2005) Intellectual Property Landscape of the Human Genome. *Science,* 310(5746): 239–240.
7. Castle, D. ed. (2006) The role of Intellectual Property Rights in Biotechnology Innovation, Edward Elgar, Northampton, MA, USA p. 101–152.
8. Soini, S., Ayme, S., and Matthijs, G. (2008) Patenting and licensing in genetic testing: ethical, legal and social issues, *European Journal of Human Genetics,* 16: 510–50.
9. Regents of the University of California (2001) Recombinant DNA Research at UCSF and Commercial Application at Genentech, Boyer's UCSF Laboratory.
10. Patzelt, H. and Brenner, T. eds. (2008) Handbook for bio tech entrepreneurs. *Springer.* New York, p. 193–207 Chapter 10.
11. Zucker, L.G., Darby, M.R. and Amstrong, J.S. (2002) Commercializing Knowledge: University Science, Knowledge Capture and Firm Performance in Biotechnology, *Management Science*, 48(1): 149–170.

12. Zechendorf, B. (2011) Regional Biotechnology - The EU biocluster study, *Journal of Commercial Biotechnology*, 17: 209–217, http://doi.org/10.1057/jcb.2011.13.

13. Pugatch, M.P., Torstensson, D. and Chu, R. (2012) Taking stock: How global biotechnology benefits from Intellectual Property Rights, *Pugatch Consilium*, 57 p.

14. OECD (2011) Intellectual Assets and Innovation, http://www.oecd-ilibrary.org/intellectual-assets-and-innovation.

15. Gambardella, A., Harhoff, D. and Verspagen, B. (2008) The value of European patents. European Management Review 5: 69–84.

16. Harhoff, D., Scherer, F.M. and Vopel, K. (2003) Citations, family size, opposition and the value of patent rights, *Research Policy.* 32: 1343–1363.

17. Harhoff, D., Narin, F., Sherer, F.M. and Vopel, K. (1999) Citation Frequency and the value of patented inventions. *The Review of Economics and Statistics*. 81(3): 511–515, doi/10.1162/003465399558265.

18. Magazzini, L., Pammolli, F. And Riccaboni, M. (2008) Patent value and R&D Competion*, DRUID Summer Conference Copenhagen.*

19. Hall, B.H, Jaffe, A. and Trajtenberg, M. (2005) Market value and patent citations. *Rand Journal of Economics*. 1–49.

20. Hall, B.H., Thoma, G. and Torrisi, S. (2007) Market value of patents and R&D; evidence from EU firms. *NBER*.

21. Hall, B., Jaffe, A. B, and Trajtenberg, M. (1998) Patent Citations and Market Value, *NBER*.

22. Gilroy, B.M., Brandes, W. and Volpert, T. (2003) Economic implications of Intellectual Property Rights for the Biotechnology sector, A comparative analysis of the European – Japanese Situations, http://mpra.ub.uni-muenchen.de/22200/.

23. Narin, F., Noma, E. and Perry, R. (1987) Patents as indicators of corporate technological strength. *Research Policy* 16: 143–153.

24. Carpenter, M.P, Narin, F. and Woolf, P. (1981) Citation Rates to Technologically Important Patents. *World Patent Information*. 3(4): 160–163.

25. Trajtenberg, M. (1990) A penny for Your Quotes: Patent Citations and the Value of Innovations. *The RAND Journal of Economics.* 21(1): 172–187.

26. Fallaux, F.J., Hoeben, R.C. Bout, B., Valerio, D. Van der Eb, A.(1995) EP0833934 Packaging Systems of human recombinant adenovirus to be used for gene therapy. https://nl.espacenet.com/EP0833934.

27. Hawk IP. (2012) What is EPODOC and what is DOCDB? http://www.hawkip.com/epodoc.

28. Munari, F., and Oriani, R. (eds.). (2011) The economic valuation of patents: Methods and Applications. Edward Elgar, Cheltenham, UK; Northampton, p. 169–199.

29. Blume, S.S. (2013) Medical innovations: Their diffusion, adoption and critical interrogation, *Sociology Compass,* 7(9): 726–737*,* http://doi.org/10.1111/soc4.12062.

30. Rogers, E.M. (2003) The Diffusion of Innovations. MacMillan Publishing C. Inc., New York, p. 271–307.

31. Kers, J.G., Van Burg, E. Stoop, T. and Cornel, M.C. (2014) Trends in Genetic patent applications; the commercialization of academic intellectual property, *European Journal of Human Genetics* 1–5, http://doi.org/10.1038/ejhg.2013.305.

32. OECD (2009) Biotechnology statistics, https://www.oecd.org/sti/42833898.pdf.

33. Kaufman (2012) Start- up act for the States, http://www.kauffman.org/startup act.pdf.

34. Anecdotal data from interviews with Crucell ex- IPR manager and inventors (2014).

35. Hoeben, R.C. (2001) 'Van kwaad tot beter' over virussen, vectoren en gentherapie. Rede uitgesproken bij de aanvaarding van het ambt van hoogleraar in de Genoverdracht aan de Universiteit Leiden (in Dutch).

36. Pardo, R., and Calvo, F. (2006) Are Europeans really antagonistic to biotech? *Nature Biotechnology*, 24(4): 393–395, http://doi.org/10.1038/nbt0406-393b.

37. Graff, G.D., Philips, D., Lei, Z. Oh, S. and Nottenburg, C. (2013) Not quite a myriad of gene patents. *Nature Biotechnology,* 31(5): 404–410, http://doi.org/10.1038/nbt.2568.

38. Editorial (2013) A Victory for Genes, *Nature Medicine,* 19: 792, http://doi.org/10.1038/nm.3279.

39. Lawrence, S. (2007) Biotech patents still strong, *Nature Biotechnology*, 25(12): 1341, http://doi.org/10.1038/nbt1207-1341.

APPENDIX 1

Used International Patent Classification Codes to Identify Life Sciences Inventions

A61B	Medical sciences, diagnostics
A61B1	idem, instruments
A61K	medical preparations
A61K31	idem, using organic substances
A61K35	idem, materials
A61K38	idem, peptides
A61K39	idem, antibodies
A61K48	gene therapy
A61K9	preparations with special form
A61P	therapeutic effects of chemical compounds or medical preparations
A61P25	idem, for the nervous system
A61P3	idem, for the metabolism
A61P35	idem, against tumours
A61P9	idem, against cardio vascular diseases
C07H	sugars with nucleic acid
C07K	peptides
C07K14	idem, having more than 20 amino acids
C07K16	idem, immunoglobulins, e.g. monoclonal antibodies
C12N	compositions of micro-organisms or enzymes
C12N15	idem, genetically modified DNA or RNA, vectors, plasmids and their isolation or preparation
C12N15/12	idem, recombinant DNA technology
C12N5	idem, undifferentiated human, animal or plant cells e.g. Cell lines, tissues
C12N5/10	idem, modified cells by the introduction of foreign genetic material
C12N9	idem, pro enzymes
C12Q	measuring processes
C12Q1	idem, with enzymes or micro organisms
C12Q1/68	idem, using nucleic acids
G01	measuring
G01N33/50	idem by analysis chemical/ physical properties using micro- organisms
G01N33/53	idem, using bio specific assays
G01N33/574	idem, bindings assays for cancer
G01N33/68	idem, using peptides, proteins or amino acids
G06F	electrical digital data processing
G06K	recognition of data and data presenting
G06T	imaging of data

APPENDIX 2

Global Landscape of Patent Applicants (per cent) in the Life Sciences and Health Sector, their Country of Origin (per cent) and Most Important Life Sciences Domains

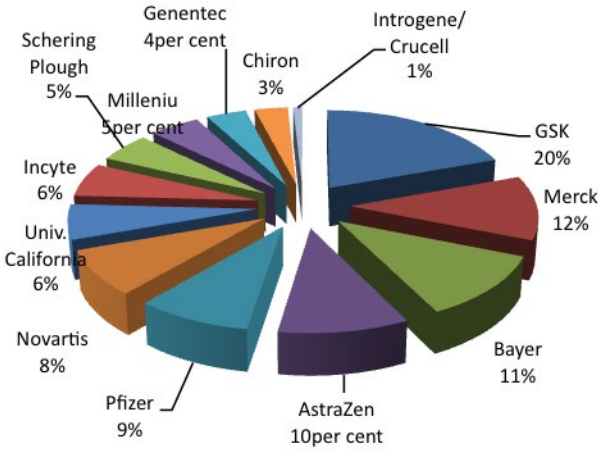


Figure A: Life sciences and health patent applicants (1995 – 2005)

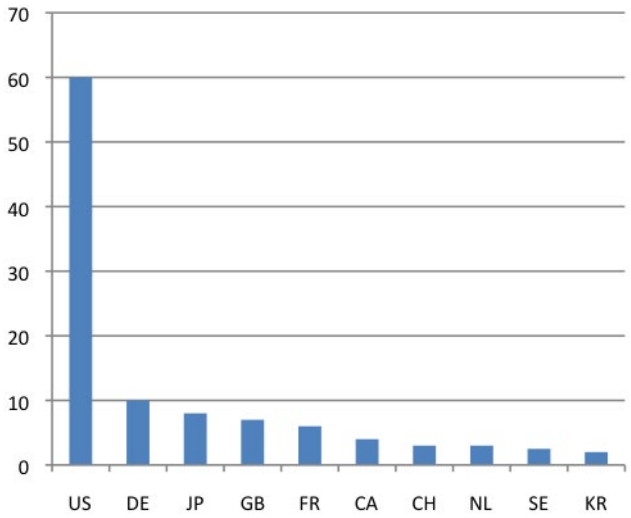


Figure B: Countries of origin for life sciences and health patent applications (1995 – 2005, in per cent)

Table A: Number and distribution of life sciences patent applications (as identified by International Patent Classification code) between 1995 and 2005 in three domains (per cent)

International Patent Classification code	Cancer	Immunology	Vaccines
Total number of patent applications (*)	36, 375	17, 348	13, 065
In percentage (per cent)			
A61K medicines	33	33,1	33,9
A61K48 gene therapy(**)	1,7	1,8	1,9
A61P therapeutic use	14,5	6,2	4,6
C07H sugars with nucleic acid	2,1	2,1	2,3
C07K peptides	7,0	13,2	15,3
C12N micro-organisms / enzymes	9,3	17,8	22,2
C12Q measurement	5,1	3,9	4,5
G01N chemical/ phys. analysis	8,7	6,6	5,9

(*) Both WO/ PCT and EP patent applications

(**) Average percentage of gene therapy patents in the three domains = 1,8 per cent

APPENDIX 3

Gene Therapy Patent Applicants, their Origin and the Granting Procedures Practices

Table A: Distribution of patent applications, inventors and licensees of gene therapy patents similar to EP 0833934 and filed in 1995

Applications by companies and universities (N= 93)		Inventors (Mentioned in N= 93 applications)		Licensees of granted patents (N= 38)	
Chiron –Viagene	17 %	H. Gruber	16 %	Oxford Biomedica Ltd.	29 %
American Cyanamid	6 %	D. Jolly	11 %	National Institutes of Health	26 %
Transgene	5 %	J. Barber	7 %	East Virginia Medical School	8 %
Genvec	5 %	I. Koveski	7 %	GBP IP	5 %
Canji	4 %	A. McCormick	4 %	Glaxo Welcome	3 %
Genetic Therapy	3 %	P. Klatzmann	4 %	US Health	3 %
Cell Genesys	3 %	W. Zhang	4 %	Texas Cancer Centre	3 %
Introgene/ Crucell	1 %	S. Woo	4 %	Others	23 %
University Paris	4 %	Others	43 %		
University Texas	4 %				
University California	3 %				
Baylor College of Medicine	3 %				
Others	42 %				
Total	100 %	Total	100 %	Total	100 %

Table B: Granting percentage of gene therapy priority patents (PAs) filed in 1995 at various patent offices

Patent Office	Granted vs. not granted PAs	Granted PAs (per cent)	Avg. time to grant after filing (years)
USPTO (USA)	60 / 10	86	< 4
European Patent Office	2 / 1	67	> 10
National Offices EU (avg.)	13 / 5	71	< 4
IL (Israel)	1 / 1	50	< 10

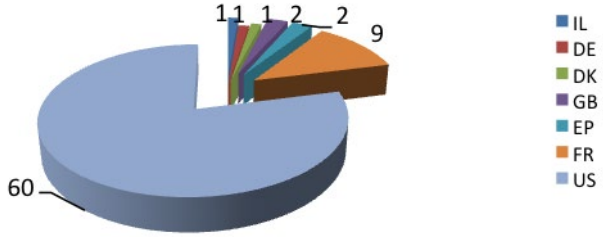


Figure A: Country or region of origin of patent (N=93) applicants in 1995 (in per cent)
IL = Israel, DE = Germany, DK = Denmark, GB = United Kingdom, EP = European, FR = France and US = United States

IP MANAGEMENT

A Biotechnology Dilemma: Patent Your Inventions (if you can) or Keep Them Secret

Craig R. Smith
is a partner at Lando & Anastasi, LLP, an Intellectual Property law firm. Mr. Smith is a trial attorney who helps clients protect and defend their inventions in complex intellectual property litigation. His practice also focuses on advising clients on post-grant patent reviews, licensing, strategic management of patent, trademark and copyright portfolios, due diligence, and pre-suit investigations.

ABSTRACT

Biotechnology companies rely on patents to protect their most valuable inventions. Patent protection helps support billions of dollars in research and development of life-saving drugs and treatments. Protecting biotechnology inventions has become more difficult in the last few years, however, because legal trends have created uncertainty regarding what subject matter is eligible for patent protection. Specifically, courts have narrowed the scope of what is patentable and have increasingly invalidated patents because they claim abstract ideas or laws of nature. As biotechnology companies wait for more clarity on the scope of patentable subject matter, they face a dilemma of whether to patent their inventions or keep them secret. Keeping inventions secret offers some benefits to companies, but may not be sufficient to protect the significant investment made in research and development. The biotechnology industry will continue to grapple with this dilemma until the courts, the Patent Office or new legislation clarifies the boundaries of what subject matter is patentable.

Journal of Commercial Biotechnology (2017) 23(2), 74–80. doi: 10.5912/jcb797
Keywords: patent; trade secret; court; natural phenomena; law of nature; Federal Circuit; Supreme Court

INTRODUCTION

Biotechnology companies rely heavily on patents to protect their most valuable inventions. Patent protection helps support billions of dollars in research and development of life-saving drugs and treatments. Protecting biotechnology inventions has become more difficult in the last few years, however, because legal trends have created uncertainty regarding what subject matter is eligible for patent protection. Specifically, courts have narrowed the scope of what is patentable and have increasingly invalidated patents because they claim abstract ideas or laws of nature. For example, courts have invalidated patents covering valuable diagnostic methods for treating Crohn's disease and screening methods for Down's syndrome. Indeed, the court that is responsible for all initial patent appeals—the Court of Appeals for the Federal Circuit—has invalidated patents in nearly 90% of decisions it has issued relating to challenges based on ineligible subject matter.

Industry groups have expressed concern regarding these patent law trends and their impact on innovation. For example, the Pharmaceutical Research and Manufacturers of America has criticized the current state of the law because it is "hard for a patentee to know which inventions are patentable or not."[1] This concern was echoed by the Intellectual Property Owners Association, which explained that "[r]ecent Supreme Court decisions … have dramatically narrowed the scope of patent protection for life sciences …"[2] And the former Director of United States Patent & Trademark Office, David Kappos, described the current situation as "the worst mess I've seen in the 30 years I've been practicing law."[3]

The uncertainty created by recent court decisions has also influenced the examination of patent applications. The United States Patent and Trademark Office closely monitors court opinions and modifies its procedures for examining patent applications accordingly. Patent applications are regularly rejected by the Patent

Correspondence:
Craig R. Smith, Lando & Anastasi, LLP, US. Email: CSmith@lalaw.com

Office for claiming laws of nature, natural phenomena, and abstract ideas. As a result, it has become more difficult for companies to predict whether the Patent Office will grant patents on certain types of inventions, including diagnostic and screening methods that include laws of nature or natural phenomena.

As biotechnology companies wait for more clarity on the scope of patentable subject matter, they face a dilemma of whether to patent their inventions or keep them secret. Patent protection creates a limited monopoly in exchange for publicly disclosing inventions to the world. This patent monopoly is critical to biopharmaceutical companies because they "rely on patents to protect their inventions and provide an opportunity to recover their R&D costs and fund new research."[4] In contrast, trade secret protection is based on keeping ideas secret from the world. Keeping inventions secret offers some benefits to companies, but may not be sufficient to protect the significant investment made in research and development. The biotechnology industry will continue to grapple with this dilemma until the courts, the Patent Office or new legislation clarifies the boundaries of what subject matter is patentable.

The full scope of this dilemma can be understood by analyzing what the law says is eligible for patent protection, how courts have interpreted the law, and why biotechnology companies and industry organizations have criticized these developments.

PATENT PROTECTION FOR ALMOST "ANYTHING UNDER THE SUN THAT IS MADE BY MAN"

The United States Constitution grants Congress the power "[t]o promote the progress of science and useful arts, by securing for limited times to … inventors the exclusive right to their … discoveries."[5] Congress has enacted legislation to help inventors protect a broad array of inventions, including *almost* "anything under the sun that is made by man."[6] The Patent Act states:

> *Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.*[7]

This broad articulation of patentable subject matter is not without limits. Courts have created exceptions to what is patentable, holding that "laws of nature, natural phenomena, and abstract ideas" are not patentable.[8] The United States Supreme Court has explained that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts are not patentable, as they are the basic tools of scientific and technological work."[9] Allowing inventors to patent these tools would likely "impede innovation more than it would tend to promote it."[10]

Defining the boundaries of these exceptions has never been easy. A natural phenomenon can be transformed into a patentable idea by human intervention. For example, a naturally-occurring micro-organism would not be patentable; however, a "human-made, genetically engineered bacterium" is eligible for patent protection.[11] The new "micro-organism plainly qualifies as patentable subject matter" because it is "a nonnaturally occurring manufacture or composition of matter—a product of human ingenuity 'having a distinctive name, character [and] use.'"[12]

New scientific discoveries challenge courts to define the boundary between what is patentable and what is not.

PATENTABLE OR NOT, THAT IS THE QUESTION

Diagnostic and Screening Methods

Until recently, the patentability of inventions was rarely challenged and courts rarely invalidated biotechnology patents based on whether they covered patentable subject matter. Instead, patents were typically challenged based on whether they claimed a new and non-obvious invention. The state of the law changed dramatically when the Supreme Court issued its decision in *Mayo Collaborative Services v. Prometheus Laboratories*.[13] Prometheus had been awarded a patent on using thiopurine drugs to treat Crohn's disease.[14] The patent claimed a method of administering 6-thioguanine to a patient and then determining the level of 6-thioguanine. Depending on the level of 6-thioguanine in the patient, the patent recommended an increase or decrease in 6-thioguanine to either improve the drug's efficacy or avoid causing harm to the patient. Prometheus alleged that Mayo infringed claims of its patent. Mayo challenged the validity of the patent, and the Court held that this diagnostic method was unpatentable.[15]

The *Mayo* decision set forth and applied a framework for evaluating whether patents claim patentable subject matter. First, a court determines whether the patent claims are directed to ineligible subject matter, such as a law of nature.[16] Second, if excluded subject matter is claimed, then the court evaluates whether the claims add something more to the otherwise ineligible

subject matter to justify patent protection.[17] Applying this analytical framework to the Prometheus patent, the Court held that the patent covered a law of nature because it described the natural "relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm."[18] Next, the Court considered "whether the claims do significantly more than simply describe these natural relations."[19] It answered this question in the negative. None of the claimed steps of the patent added enough to the natural law to make the claim patentable.[20]

The far-reaching implications of the Supreme Court's decision in *Mayo* were immediately evident, even to the Court itself. A broad application of the natural law exclusion called into question the validity of many diagnostic patents. The Court recognized that "too broad an interpretation of this exclusionary principle could eviscerate patent law"[21] because "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas."[22]

After *Mayo*, lower courts have more frequently invalidated patents relating to diagnostic or screening methods. In *PerkinElmer v. Intema*, for example, the Federal Circuit held that a screening method for Down's syndrome was unpatentable.[23] Itema had patented screening methods to determine "whether a pregnant woman is at an increased risk of having a fetus with Down's syndrome."[24] This new, non-invasive screening method was a significant advancement over invasive diagnostic methods that increased the risk of miscarriage. Nevertheless, the court held that the patent claims covered ineligible subject matter because they described a law of nature—"the relationship between screening marker levels and the risk of fetal Down's syndrome"—and included "the mental process of comparing data to determine a risk level."[25] In examining the claims, the court was unable to find a specific inventive application that was more than the ineligible natural law and mental step.[26] Accordingly, the patent was held invalid for covering ineligible subject matter.

The Federal Circuit has invalidated nearly all of the patents that have been challenged since *Mayo* based on ineligible subject matter.[27] *Mayo's* broad definition of "laws of nature" has "decimated patents and pending patent applications directed to diagnostic methods."[28] These decisions have resulted in a substantial loss of valuable patent protection.

Naturally Occurring DNA Segments

Shortly after *Mayo*, the Supreme Court decided an important case relating to the patentability of natural phenomena – one that again narrowed what biotechnology discoveries can be patented. In *Myriad Genetics*, the Court held that naturally occurring DNA segments are not patentable, but complementary DNA (or cDNA) are patentable.[29] Myriad discovered the BRCA1 and BRCA2 genetic mutations that increase the risk of breast cancer and ovarian cancer.[30] The importance of this discovery was beyond dispute, but the Court noted that a "[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the" question of whether the invention is eligible for patent protection.[31] In other words, even a remarkable discovery of a natural phenomena is not necessarily patentable.

Some of Myriad's patent claims covered naturally occurring genetic sequences. These genetic sequences are products of nature.

> *The location and order of the nucleotides existed in nature before Myriad found them. Nor did Myriad create or alter the genetic structure of DNA. Instead, Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13.*[32]

Because "Myriad did not create anything," it was not entitled to patent protection on the naturally occurring genetic sequences.[33]

The Court distinguished cDNA from the genetic sequences held ineligible because cDNA is not naturally occurring. "[C]reation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring."[34] As a result, cDNA is eligible for patent protection if it is different from the naturally occurring genetic sequence.[35]

Other medically significant discoveries have been deemed unpatentable based on the reasoning in *Mayo* and *Myriad*. In *Ariosa*, the Federal Circuit held that a method of detecting cell-free fetal DNA (or cffDNA) was unpatentable.[36] Two doctors discovered paternally inherited cffDNA in blood samples of pregnant women.[37] The cffDNA can be used to determine characteristics of the fetus, including gender. It was "undisputed that the existence of cffDNA in maternal blood is a natural phenomenon."[38] Even though Sequenom's patent claims did not cover cffDNA, but methods of using cffDNA, the claimed methods "are generally directed to detecting the presence of a naturally occurring thing or a natural phenomenon, cffDNA in maternal plasma or serum."[39] The remaining steps of the claims were "well-understood, conventional

and routine" techniques for "detecting paternally inherited cffDNA."[40] As a result, the court concluded that the claims failed to disclose patent eligible subject matter.[41]

One of the judges responsible for the *Ariosa* decision expressed concern that *Mayo's* broad language is "excluding a meritorious invention from the patent protection it deserves and should have been entitled to retain."[42] According to Judge Lynn, "[b]ut for the sweeping language in the Supreme Court's *Mayo* opinion, I see no reason, in policy or statute, why [Sequenom's] breakthrough invention should be deemed patent ineligible."[43]

Sequenom requested a rehearing of its appeal, but the request was denied.[44] Several judges on the Federal Circuit took this denial as an opportunity to criticize the state of the law. Judge Lourie commented that there is "some truth in [the] concern" that a "whole category of diagnostic [patent] claims is at risk"[45] because of the Supreme Court's decision in *Mayo*. "In sum, it is unsound to have a rule that takes inventions of this nature out of the realm of patent-eligibility on grounds that they only claim a natural phenomenon plus conventional steps, or that they claim abstract concepts."[46] Judge Dyk shared the concern that the current state of the law "may discourage development and disclosure of new diagnostic and therapeutic methods in the life sciences, which are often driven by discovery of new natural laws and phenomena."[47] He criticized the *Mayo* decision because it potentially precludes too many inventions from patent protection.

> *Mayo did not fully take into account the fact that an inventive concept can come not just from creative, unconventional application of a natural law, but also from the creativity and novelty of the discovery of the law itself. This is especially true in the life sciences, where development of useful new diagnostic and therapeutic methods is driven by investigation of complex biological systems. I worry that method claims that apply newly discovered natural laws and phenomena in somewhat conventional ways are screened out by the Mayo test.*[48]

Finally, Judge Newman argued that the case was "wrongly decided" and that the diagnostic method should be eligible for patent protection because it is "novel and unforeseen, and is of profound public benefit—'a significant contribution to the medical field,'…—a 'breakthrough.'"[49]

GROWING CONCERN IN THE BIOTECHNOLOGY INDUSTRY

The biotechnology industry, along with many organizations, has raised concerns regarding the current trend in patent law. Recently the United States Patent and Trademark Office (PTO) requested public comments relating to patent eligibility.[50] Several organizations responded. The Pharmaceutical Research and Manufacturers of America (PhRMA) explained that "the current jurisprudence is not protecting important advances for patients and thus could stifle future innovation to produce new drugs and treatments."[51] The Supreme Court's "Mayo analysis sweeps too broadly and invalidates important contributions to society in this area that the patent system was designed to protect."[52]

The American Bar Association (ABA) has also criticized the trend in patent ineligibility.[53] The ABA is concerned that the current interpretation of the law stifles the "incentive to innovate."

> *The current jurisprudence on patent eligibility under section 101 is confusing, creates uncertainty as to the availability and enforceability of patent assets, arguably risks the incentive to innovate provided by patents in technologies in which U.S. industry has historically led the world, and potentially places the U.S. in a less advantageous position on patent protection than our leading competitor nations.*[54]

Similarly, the IPO has concluded that "[a]n overly broad view of the exceptions to patent eligible subject matter undermines incentives to invest in or develop new drugs and treatment methods."[55]

These concerns not only apply to existing patents challenged in court, but also to applications filed with the United States Patent Office for patent approval. The Patent Office has followed the recent trends in the law and has adjusted its patent examination guidelines based on them.[56] As a consequence, the uncertainty created by courts has resulted in more patent applications being rejected by the Patent Office for claiming unpatentable subject matter. The AIPLA has raised concerns with the Patent Office, stating that its "examination decisions on patent eligibility have been inconsistent and confusing."[57] When the PTO rejects an application based on ineligible subject matter, it becomes an "an insurmountable barrier"[58] to obtaining patent protection. Thus, the ability to protect future inventions is at risk.

A LEGISLATIVE SOLUTION

Several organizations have expressed concern that the current state of the law cannot be fixed by the courts, and that a legislative solution is required. The ABA has argued that "further judicial interpretation is unlikely, in the foreseeable future, to rectify the ambiguities and uncertainties created by that jurisprudence."[59] Instead, the ABA recommends "legislation clarifying the distinct role for section 101 in limiting patent eligibility to practical uses of processes, machines, manufactures, and compositions of matter."[60] Likewise, the AIPLA has argued that "a legislative solution is needed that will help increase certainty and efficiencies in our patent system and promote innovation in the United States."[61]

Most of the legislative solutions that have been recommended focus on overruling the current *Mayo* test for patent eligibility. In its place would be an arguably simpler test that would allow more inventions to be considered patent eligible. For example, the IPO has recommended that there be only two narrow exceptions to patent eligibility:

> *A claimed invention is ineligible under subsection (a) if and only if the claimed invention as a whole, as understood by a person having ordinary skill in the art to which the claimed invention pertains, exists in nature independently of and prior to any human activity, or exists solely in the human mind.*[62]

The first exception prohibits a patent on naturally occurring phenomena that have existed prior to any human activity. The second exception applies to abstract ideas that exist solely in the human mind. Each of these exceptions can be interpreted narrowly to effectively overrule the Court's recent decisions on unpatentable subject matter.

Other organizations have recommended different amendments to the Patent Act. The ABA has proposed a legislative change that would only preclude patent protection for inventions that "preempt the use by others of all practical applications of a law of nature, natural phenomenon, or abstract idea."[63] In other words, inventions that preempt some, but not all, practical applications of a law of nature would be eligible for patent protection. The legislation clarified that "[p]atent eligibility under this section shall not be negated when a practical application of a law of nature, natural phenomenon, or abstract idea is the subject matter of the claims."[64] Like the IPO proposal, the ABA's proposed legislation would allow many more inventions to be considered eligible for patent protection.

No legislation is currently under consideration by Congress.

TRADE SECRET PROTECTION

The current uncertainty in patent law has renewed discussions of using trade secret law, instead of patents, to protect the value of new discoveries and inventions. If companies are unable to obtain patent protection on their inventions, or are uncertain whether patents will survive a court challenge, they may consider using trade secret protections. A shift to trade secret protection would impact not only internal corporate policies, but may also have broader implications for the public dissemination of scientific discoveries and investment in research and development.

A trade secret can be any valuable information. In other words, a trade secret does not need to rise to the level of a novel or patentable invention. Although "[a]n exact definition of a trade secret is not possible,"[65] trade secrets are defined broadly to include information that derives economic value from being generally unknown and is subject to reasonable efforts to keep them secret. The Uniform Trade Secrets Act defines a trade secret as:

> *information, including a formula, pattern, compilation, program, device, method, technique, or process, that:*
>
> 1. *derives independent economic value, actual or potential, from not being generally known to, and not being readily ascertainable by proper means by, other persons who can obtain economic value from its disclosure or use, and*
> 2. *is the subject of efforts that are reasonable under the circumstances to maintain its secrecy.*[66]

Companies that rely on trade secret protection must be vigilant in their efforts to identify economically valuable secrets and institute procedures to maintain their secrecy.

There are several tradeoffs to consider when determining whether to rely on trade secret protection. Unlike patent protection, which requires the public disclosure of the invention, trade secret protection relies on secrecy. Patent protection represents a deal made with the government: in exchange for publicly disclosing a discovery, the inventor is entitled to a limited monopoly on the invention. The monopoly allows the patent holder to exclude others from using the invention during the term of the patent. In contrast, a trade secret is valuable because others do not know it and therefore cannot use it. A trade secret can last forever, provided that it is kept secret. In other words, trade secrets are fragile;

they must be protected. Disclosure of the trade secret can destroy the secret. For example, if companies need to disclose certain trade secrets in order to obtain regulatory approval from the government, then the secret may be lost, along with its economic value.

Biotechnology companies have expressed concern that trade secret protection is an inadequate substitute for patent protection. PhRMA has indicated that trade secret protection "is an unrealistic option for the biopharmaceutical sector."[67] For inventions that can be reverse engineered or must be disclosed to regulatory agencies, trade secret protection is not an option. These types of inventions require patent protection to justify the significant investment in research and development.

> *[Pharmaceutical companies] rely on patents to protect their inventions and provide an opportunity to recover their R&D costs and fund new research. Patents are critical for biopharmaceutical innovation given the research-intensive nature of this sector and the substantial upfront investment needed to discover and develop products that meet FDA approval requirements.*[68]

A shift to trade secret protection could result in "less disclosure of technologies and less of an incentive for innovation of important biopharmaceutical technologies for patents."[69] If patent protection becomes a less viable means of protecting inventions, then companies may choose to keep inventions secret. "Patent laws provide an incentive to disclose inventive technology that is beneficial to the public, whereas trade secret protection relies on maintaining the secrecy of the technology."[70]

Without patent protection, some companies may face more challenges in securing necessary investments for research and development. The ABA has raised concerns regarding the loss of investments in the absence of patent protection: "without patents, emerging businesses and universities would be at risk with respect to their ability to attract needed investment."[71]

CONCLUSION

In the past five years, the biotechnology industry has faced a seismic shift in the state of patent law, calling into question what inventions are eligible for patent protection. Patents relating to diagnostic and screening methods have been invalidated and patent protection has become more unpredictable. These developments in patent law have forced biotechnology companies to reevaluate patent protection and consider whether trade secret protection provides an adequate remedy. Without patent protection, however, companies may be less willing to invest in certain research and development, and less likely to publicly disclose their discoveries. Both results would potentially limit innovation.

ENDNOTES

1. Comments of the Pharmaceutical Research and Manufacturers of America (PhRMA) Responding to the United States Patent and Trademark Office's Notice of Roundtables and Request for Comments Related to Patent Subject Matter Eligibility, Docket No.: PTO-P-2016-0041, January 18, 2017 ("PhRMA Comments"), at 7.
2. Intellectual Property Owners Association (IPO), Section 101 Legislative Task Force, "Proposed Amendments to Patent Eligible Subject Matter Under 35 U.S.C. 101," February 7, 2017 ("IPO Comments"), at 1.
3. David Kappos, Federal Circuit Judicial Conference, Washington, D.C., April 2016.
4. PhRMA Comments, at 2.
5. United States Constitution, Article I, Section 8, Clause 8.
6. *Diamond v. Chakrabarty,* 447 U.S. 303, 309 (1980) (quoting the Committee Reports accompanying the 1952 Act, S.Rep.No.1979, 82d Cong., 2d Sess., 5 (1952); H.R.Rep.No.1923, 82d Cong., 2d Sess., 6 (1952)).
7. 35 U.S.C. § 101.
8. *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 566 U.S. 66, 70 (2012) ("*Mayo*") (quoting *Diamond v. Diehr*, 450 U. S. 175, 185 (1981)).
9. *Gottschalk v. Benson*, 409 U. S. 63, 67 (1972).
10. *Mayo,* 566 U.S., at 71.
11. *Chakrabarty,* 447 U.S., at 309-310.
12. *Chakrabarty,* 447 U.S., at 309-310 (quoting from *Hartranft v. Wiegmann*, 121 U. S. 609, 615 (1887)).
13. *Mayo,* 566 U.S. 66.
14. *Mayo*, 566 U.S., at 73.
15. *Mayo*, 566 U.S., at 92.
16. *Mayo*, 566 U.S., at 77.
17. *Mayo*, 566 U.S., at 77.
18. *Mayo*, 566 U.S., at 77.
19. *Mayo*, 566 U.S., at 77.
20. *Mayo*, 566 U.S., at 77-80.
21. *Mayo*, 566 U.S., at 71.
22. *Mayo*, 566 U.S., at 71.
23. *PerkinElmer, Inc. and NTD Laboratories, Inc. v. Intema Limited*, 496 Fed. Appx. 65 (Fed. Cir. 2012)
24. *PerkinElmer,* 496 Fed. Appx., at 67.

25. *PerkinElmer,* 496 Fed. Appx., at 70.
26. *PerkinElmer,* 496 Fed. Appx., at 71-72.
27. AliceStorm Update for Q1 2017, http://www.bilskiblog.com/blog/alicestorm (April 7, 2017)
28. IPO Comments, at 12.
29. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2111 (2013)("*Myriad*").
30. *Myriad*, 133 S. Ct., at 2112-13.
31. *Myriad*, 133 S. Ct., at 2117.
32. *Myriad*, 133 S. Ct., at 2116.
33. *Myriad*, 133 S. Ct., at 2117.
34. *Myriad*, 133 S. Ct., at 2119.
35. *Myriad*, 133 S. Ct., at 2119.
36. *Ariosa Diagnositics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015).
37. *Ariosa*, 788 F.3d, at 1373.
38. *Ariosa*, 788 F.3d, at 1376.
39. *Ariosa*, 788 F.3d, at 1376.
40. *Ariosa*, 788 F.3d, at 1377.
41. *Ariosa*, 788 F.3d, at 1378.
42. *Ariosa*, 788 F.3d, at 1380 (Lynn, J., concurring).
43. *Ariosa*, 788 F.3d, at 1381 (Lynn, J., concurring).
44. *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 809 F.3d 1282 (Fed. Cir. 2015) (order denying request for *en banc* hearing)("*Ariosa En Banc Denial*").
45. *Ariosa En Banc Denial,* 809 F.3d 1282, 1285 (Lourie, J., concurring).
46. *Ariosa En Banc Denial,* 809 F.3d 1282, 1287 (Lourie, J., concurring).
47. *Ariosa En Banc Denial,* 809 F.3d 1282, 1287 (Dyk, J., concurring).
48. *Ariosa En Banc Denial,* 809 F.3d 1282, 1289-90 (Dyk, J., concurring).
49. *Ariosa En Banc Denial,* 809 F.3d 1282, 1294 (Newman, J., dissenting).
50. United States Patent and Trademark Office's ("USPTO's") Notice of Roundtables and Request for Comments Related to Patent Subject Matter Eligibility, 81 Fed. Reg. 71485-71489 (October 17, 2016).
51. PhRMA Comments, at 6.
52. PhRMA Comments, at 8.
53. American Bar Association Comments Related to Patent Subject Matter Eligibility, January 18, 2017 ("ABA Comments").
54. ABA Comments at 2.
55. IPO Comments, at 26.
56. United States Patent & Trademark Office Guidelines on Subject Matter Eligibility, https://www.uspto.gov/patent/laws-and-regulations/examination-policy/subject-matter-eligibility
57. Comments of the American Intellectual Property Law Association (AIPLA) on Notice of Roundtables and Request for Comments Related to Patent Subject Matter Eligibility, 81 Fed. Reg. 71485, October 17, 2016 ("AIPLA Comments"), at 1.
58. AIPLA Comments, at 2.
59. ABA Comments, at 3.
60. ABA Comments, at 3.
61. AIPLA Comments, at 3.
62. IPO Comments, at 1
63. American Bar Association letter to Michelle Lee, dated March 28, 2017, regarding "Supplemental Comments Related to Patent Subject Matter Eligibility," ("ABA Letter"), at 3.
64. ABA Letter, at 3.
65. *Restatement of Torts*, Section 757, comment b.
66. *Uniform Trade Secrets Act*, Section 1(4)(1985).
67. PhRMA Comments, at 8.
68. PhRMA Comments, at 2.
69. PhRMA Comments, at 8.
70. PhRMA Comments, at 8.
71. ABA Comments, at 1.

Journal of
COMMERCIAL
BIOTECHNOLOGY
http://CommercialBiotechnology.com

PUBLISHER

The *Journal of Commercial Biotechnology* is published quarterly in Washington, DC by thinkBiotech LLC.

The *Journal of Commercial Biotechnology* is available online at *http://www.CommercialBiotechnology.com*. Visit the journal's website for focus, scope, and policies; submission guidelines; sample papers; and staff contacts. The website may also be used to order subscriptions.

CORRESPONDENCE

Business correspondence and inquiries should be addressed to *editor@CommercialBiotechnology.com* or to thinkBiotech LLC, 1133 15th Street NW, 12th Floor Washington, DC 20005.

CUSTOMER SERVICE AND SUBSCRIPTION INQUIRIES

Susbcription policies and rates are posted at *http://www.CommercialBiotechnology.com/about/subscriptions*.

Subscriptions may be purchased by following the above link, or by sending a check, money order, or credit card details to the correspondence address above. Purchase orders, invoice requests, and additional questions may be directed to *editor@CommercialBiotechnology.com*.

2017 Subscriptions		
Student	Digital	US$169
Individual	Digital	US$225
	Print + Digital	US$280
Small company < 100 employees	Digital	US$560
Institutional	Digital	US$1060
	Print + Digital	US$1120

ADVERTISING

A media kit with advertising rates is posted at *http://www.CommercialBiotechnology.com/JCB-mediakit.pdf*.
Additional questions may be directed to *editor@CommercialBiotechnology.com*.

REPRINTS

For reprints of this journal please contact the publisher at the address above or at *editor@CommercialBiotechnology.com*.

PERMISSIONS

For queries relating to reproduction rights please contact the publisher at the address above or at *editor@CommercialBiotechnology.com*.

COPYRIGHT

Print ISSN: 1462-8732
Online ISSN: 1478-565X