Understanding Medical Device Patenting and Clinical Trials for Product Leadership

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Abstract--**Unmet clinical needs remain the primary driving force for innovations in medical devices. While appropriate mechanisms to protect these innovative outcomes are essential, the performance of clinical trials to ensure safety is also mandated before the invention is ready for public use. Literature explaining the relationship between patenting activities and clinical trials of medical devices is scarce. Linking patent ownership to clinical trials may imply product leadership and value chain control. In this paper, we use patent data from Indian Patent Office (IPO), PCT, and data from Clinical Trials Registry of India (CTRI) to identify whether patent assignees have any role in leading as primary sponsors of clinical trials. A total of 42 primary sponsors are identified from the CTRI database in India. Number of patents awarded to these primary sponsors in the particular medical device, total number of patents awarded to the primary sponsor in all technologies, total number of patents in the specific medical device technology provides an indication of leadership and control in the value chain.**

I. INTRODUCTION

Scientific activities are perennial in technologies striving to address the crucial needs of human beings. Though specific regions of world produce enormous amounts of technologies on a yearly basis, global needs for improved healthcare is still unmet. Considering the diversification in economic, environmental, ethnic, social and legal restrictions prevalent across the nations, manufacture of affordable, safe and compatible healthcare products becomes a risky endeavour. In developing economies like India, where affordability of safe healthcare products is of primary concern, intensified R&D activities, mass production of pharmaceuticals and medical device industries are of utmost importance. The medical device industry has not grown unlike the case of the pharmaceutical industry in India. The Indian medical device market witnesses rapid growth, but is heavily dependent on foreign countries for imports especially from US, Japan and Germany [8].

A medical device is defined as "any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article to be used, alone or in combination for human beings for one or more of the specific purpose of diagnosis, prevention, monitoring, treatment or alleviation of disease or an injury to support or sustain life", (Indian Medical Device Regulation Bill, 2006). Medical devices, in general are classified into invasive and non-invasive devices. While invasive devices need clinical trials to be performed, non-invasive ones require clinical trials only if they also are medical devices of high risk levels.

The clinical trials stage ensures the safety and efficacy of medical devices. This stage has prominent importance for successful launching of any medical device. Trials involve huge investments, human resource (medical experts and patients/subjects) and time within a rigorous regulatory framework. Given the complexity of this rigor, not many organizations, may it be a company, research laboratory, hospital, or university find it easy to carry out clinical trials. Since the rigor associated with clinical trials is high, the organization that controls the operations of the trials must know the process involved. The clinical trial stage includes actors like primary sponsors (PS) who hold the primary controls of the administration of clinical trials. The principal investigators (PI's), namely medical doctors, conduct the clinical trial for the PS. At times the PS and the PI may be from the same organization and at other times they may not be.

Additional to the apparent controls required to manage the clinical trials of a medical device, it is possible that the PS is also in control of the R&D work involved in creating the medical device. In this paper we attempt to explore the patent ownership of a PS. We use patent ownership for the medical device being tried as a strength of R&D of the PS. Linking the PS with controls over patents for their medical device, and their authority over the clinical trial operation is used as a surrogate measure of leadership in the value chain.

Accordingly, this paper is structured as follows. The section II describes literature which provides a back ground for our research. In section III we provide information on data, variables, and analysis plan including descriptive statistics and multiple regression technique for the study. We present empirical findings in section IV and summarize the results in section V.

II. LITERATURE REVIEW

The literature review in this paper discusses the medical device value chain, the number of participants and locations for conducting clinical trials and the link between patents and medical device clinical trials.

A. Medical device value chain

The value chain in the context of business organizations describes a wide range of activities which are essential for any product or a service to proceed from ideation/conception through stages of production, manufacturing, market launch and final product disposal [12,17]. The concept of value chain can be applied to various sectors. The stages in the value chain vary from domain to domain or product to

product [4,12]. For example, in healthcare it can be a stent, catheter or disposable syringe.

The medical device product life cycle can be split into five stages [19]: (i) *Concept stage* - to conceive an idea for an unmet clinical need; (ii) *Design stage* - involve device development process from (re)design to prototype; (iii) *Testing and trials stage* - prototype testing in-house and trials in real field (clinical trials); (iv) *Production stage* - includes production on large scale (manufacturing) supported by business and commercial rationale; and (v) *Deployment stage* - includes marketing, launch and use of the device in the real field.

A common pattern of six phases which occur in the medical device development process as identified by some researchers [14] are: funding phase, concept phase, development phase, verification and validation phase, product phase, and market release phase. Using the phases recognized by Panescu [14], Ham [9] attempted to create an in-depth visual map for medical device development cycle to understand the processes such as research, innovation, development, testing and trials (clinical trials), regulation, and marketing with the help of process mapping technique.

B. Participant recruitment and location

Once the R&D stage is done for an unmet clinical need, the prototype is developed. Then the prototype goes to the clinical trials stage. After successful completion of clinical trials and iterations to the prototype, the final product is mass manufactured. The device is then ready to be retailed in the market. Whilst the R&D stage poses uncertainty and risk to R&D investors, a similar situation is also seen with clinical trials. The "clinical trial" stage is very crucial and poses greater financial risk for developers of a new device [11,19,16]. Often, the clinical trial stage is referred to as a "road block" as it requires many regulatory hurdles to pass through depending on the risk of the medical device. Clinical trials are important because it helps the investigators find out which treatment is more effective than others and this is the best way to identify an effective new treatment [1].

The clinical trial is a controlled experiment performed on human subjects [18]. It is a scientific term used for examining a new medical device and to evaluate the safety and efficacy of the same [15]. The five major stakeholders involved for any clinical trial are sponsor, clinical investigator, regulatory authority, ethics committee and trial subjects/patients [6].

Subjects/patients may be recruited by sponsors, contract research organizations, clinical investigators, research coordinators and patient recruitment firms to participate in clinical research studies. Even though large number of clinical trials and population-based studies has been conducted, the amount of information that has been published regarding the recruitment of required number of participants within expected time duration is limited [10]. To execute a robust clinical trial process, a major challenge is to select appropriate study subjects to conduct clinical trials [10,20].

Participant enrolment for clinical trials is a central management function which has greater impact on the cost and time taken for the development of a medical device [17]. Also, for a successful conduction of clinical trials, achieving adequate participant enrolment rate is a major challenge [7]. For speeding up the medical device development process, selecting qualified clinical trial locations which recruit appropriate participants becomes very attractive to sponsors [2].

C. Patent protection and clinical trials

Patent protection is very important prior to market entry. Like-wise, patent protection is very important for the globalization of clinical trials [2]. Authors state that patentability for medically-related products involves patentability of surgical tools and equipments or medical devices. The sponsors who are responsible and accountable to conduct a clinical trial are more likely to consider the impact of patent protection as a broad investment strategy including the final marketing of the product [17].

Patent data provides a valuable source of information which can be used to track evolution of technological strategy of innovative firms [13]. Patentability also drives globalisation of clinical trial sites (multiple country locations) [2]. Studies indicate that physicians contribute directly to the medical device innovation process because of their best knowledge about unmet clinical needs (medical device patent data from 1990-1996). Also, physician's involvement in activities such as product testing and clinical trials can transfer information to commercializing firms which helps facilitate innovative medical devices [5].

In a comparative study carried out between Medtronic's patents and Siemens–Pacesetter in the pacemaker device sector, patent citation ratio is used as one of the measures to identify higher quality patents. The study reveals that patents owned by Medtronic's appear to be of higher quality than patents owned by Siemens–Pacesetter, which eventually fetched higher income after a law suit [3].

Literature selected in the context of this paper implies that the primary sponsor or PS can be an R&D leader as well as one who controls the clinical trials for the given device that they innovated. Given the fact that they have patents for the device they intend to try in clinical trials it is clear that they will have much control over the value chain implying also that they may have control over the market. On the other hand those in the value chain who are specialists, thus only operating either, in the clinical trial activity or only controlling R&D may not have as much controls over the value chain.

III. METHODOLOGY

The data, namely the sample, the variables used, the conceptual grouping of primary sponsors and analysis conducted is described in this section.

A. Data

For the purpose of this study data related to medical device clinical trials in India was collected from the Indian CTRI (Clinical trial registry of India) database. This database consists of medical devices and drugs. The CTRI database gives information on the primary sponsor (PS), secondary sponsor (SS), principal investigator (PI), phase of the trial, number of participants enrolled for a clinical trial, number of locations in which the clinical trial is carried out, estimated duration of the trial, public and scientific title of the study and many other variables. Additional information on the category of PS and type of device is classified by us. Patent databases such as WIPO/PCT and Indian Patent Office are used to retrieve data on a given PS. The total number of patents awarded to these PS in different technologies is considered.

The sample for this study is identified through an intense keyword search, where out of 279 records in the CTRI database 59 were identified as medical device clinical trial registrations from the year 2008 to 2012 (the rest of them were drugs hence omitted for this study). Each clinical trial registration has a PS mentioned in the data field. The PS is the one who is responsible and accountable for the clinical trial. The PS can be either from a company or medical college or hospital. A total of 59 PS are identified. Some of the PS have multiple clinical trial registrations. Hence, 42 unique PS were identified and the same are used to retrieve patent data.

In order to retrieve patent data of PS, each PS name was given in the PCT and IPO databases to identify the total number of PCT applications owned by a PS. The number of patents at the PCT website with the PS or with their subsidiaries is summed up to represent the PCT application count of the PS. Also the number of patents (patents/IPO) a PS has in Indian patent office was retrieved.

Out of the 42 PS, 30 are from companies, 6 are from medical colleges, 4 are from hospitals and 2 are from government organizations. Thirty out of 42 PS have patents only in PCT and 11 of them have patents in both PCT as well as in IPO. Medical colleges and hospitals do not have any patents in both the databases except in one case. Medtronic is the company which is leading with maximum number of patents followed by Boston Scientific, Johnson & Johnson, St. Jude Medical, and Biotronik.

The main focus of this study is to capture the influence of linking patent ownership to clinical trial sponsorship, as a surrogate of product leadership and value chain control. Variables namely number of locations a clinical trial is carried out (y_1), and number of participants in clinical trials (y_2), determine medical device importance and market potential. So for this paper these two variables are considered as dependent variables. It is assumed that the PS who is in control of the research and clinical trial value chain will also use a large number of locations and participants in their trials. Implying that such type of PS are financially sound. If the financial strength of the PS did not determine the number of locations and participants, then the type of device might determine this. The independent variables considered for this study are category of PS (x_1), type of device (x_2), number of PCT applications of the PS(x_3) and number of patents/IPO of the PS (x_4).

B. Variable description

A description of variables considered for analysis in this paper are enumerated as follows.

- *Primary sponsor (PS):* The primary sponsor of a clinical trial is considered responsible to ensure that the trial is properly registered and executed. The primary sponsors can be a company, a medical college, research institute, hospital or a government organization.
- *Type of device:* The medical device for which the clinical trial is executed can be either an invasive device or a non-invasive device.
- *Number of patent/PCT's:* The total number of PCT applications a PS has.
- *Number of patents/IPO:* The total number of patents a PS has in the IPO.
- *Number of participants:* The total number of participants (patients/subjects) recruited for a specific clinical trial to examine a new treatment.
- *Number of locations:* It denotes the location where the clinical trial is carried out in order to test the new device or treatment on participants.

C. Conceptual grouping of the PS

Based on literature emphasizing the crucial roles of patent protection and clinical trials [2,17] in medical device technologies, the PS are grouped by us into four, viz., incumbent, indigenous, potential entrant and supporter. An incumbent is considered to be a PS who has patent protection (in terms of PCT applications, and IPO patents) and executes clinical trials for a specific medical device. The indigenous PS is a type of PS who has patent protection (only in terms of Indian patents, IPO patents only) and executes clinical trials for a specific medical device. A potential entrant is considered to be a PS having patent protection only in terms of PCT applications (without any Indian patents, IPO patents) and executes clinical trials for a specific medical device. A supporter is one who does not have a patent protection but executes the clinical trials alone for any medical device. From our data we have 18 incumbents, 27 potential entrants and 14 supporters and analysis is done amongst these three groups. We do not have any indigenous PS. Table 1 shows the sample.

TABLE 1: CONCEPTUAL GROUPING OF PS

	PCT	IPO	Clinical trial
Incumbent	X	X	X
Indigenous	-	X	X
Potential entrant	X	-	X
Supporter	-	-	X

D. Analysis

The analysis is done in two stages. First, is the descriptive analysis of the patent and clinical trial data of the three groups of PS. Secondly, regression models were run to capture the relationship between patents and clinical trial data on the number of locations and number of participants. The independent variables considered for regression analysis were category of primary sponsor (x_1), type of device (x_2), number of patent/PCT (x_3) and number of patents/IPO (x_4). The dependent variable for the first regression model is the number of locations (y_1) in which the clinical trials were carried out (model 1). For the second regression model, the dependent variable considered is the number of participants (y_2) (model 2).

The regression models with number of locations as dependent variable is expressed as in equation (i) and equation (ii):

Model 1: $y_1 = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4$ … (i)

Model 2: $y_2 = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4$ … (ii)

IV. RESULTS

The results are organized into 2 sections. The first section gives the descriptive statistics of patent and clinical trial variables. In the second section, results of the two regression models built in our study to understand the relationship between the independent variables and dependent variables (viz. number of locations and number of participants) are explained.

A. Descriptive statistics of PS groups

Results of descriptive statistics of number of PCT applications, number of patents/IPO and clinical trial variables like number of participants and number of locations in which the clinical trials are carried out, is shown in Table 2 below.

It can be observed that mean values of the PS group "incumbent" is higher than "potential entrant", followed by "supporter" in number of participants and patents. Since the medical devices tried vary across the PS groups we are cautious about our inference. Nevertheless, the incumbent who is in control of the trials, has PCT applications and patents/IPO appears to field more participants. It is important to understand if this is merely due to the market leadership and commercial capabilities of the incumbent or the device type they try in clinical trials. Strangely the number of locations in India where trials are run does not vary amongst the three groups. It is also interesting to observe that average number of PCT applications and patents/IPO owned by incumbents is far higher than the other two groups implying better product leadership potential of the incumbent.

B. Regression models

In this section, we explain the results of statistical test we performed to verify whether there exists any statistically significant relation between independent variables and dependent variables (viz. number of locations and number of participants). Results of the regression analysis are summarized in Table 3 and Table 4.

Model 1 for number of locations:

Table 3 provides the regression result of the final model 1, described in equation (i). The dependent variable is the number locations used by the PS. Since the data on number of locations is skewed to the right, we transformed the number of locations by taking its logarithmic value. We regressed the independent variables on to the log transformed number of locations. It can be inferred that most of the independent variables considered for the model did not have a significant influence on the dependent variable. The adjusted R-square value was estimated to be 0.205. Of the two variables that exhibited influence on the dependent variable one was related to category of primary sponsor. One of the categories of primary sponsor that is medical colleges had significant negative influence on number of locations where the clinical trial is executed. This signals that medical colleges vary in their execution of clinical trials in terms of number of locations in comparison to companies, hospitals or government organizations. Further investigations can be aimed at understanding what aspects of medical colleges are responsible for these patterns in number of locations where clinical trials are executed. Device category, namely type of device had significant influence on number of locations where clinical trials are carried out. It is noteworthy that type of device (invasive) has significant influence on number of locations, and this is a hypothesis that needs further investigation. Clinical trials on non-invasive medical devices were executed in lesser number of locations compared to invasive medical devices. No variables related to intellectual property protection were found to have significant influence on number of locations.

TABLE 2: DESCRIPTIVE STATISTICS OF PS GROUPS*

Primary sponsors group	Total sample size (n=59)	Number of participants Mean (SD)	Number of locations Mean (SD)	Number of PCTs Mean (SD)	Number of patents in IPO Mean (SD)
Incumbent	18	694 (1516.75)	4 (4.53)	1960 (3995.69)	15 (57.62)
Potential entrant	27	476 (810.32)	4 (4.6)	881 (2256.43)	4 (16.04)
Supporter	14	470 (812.54)	4 (7.43)	878 (2526.4)	2 (5.77)

*Figures are rounded off to the nearest whole number

TABLE 3: REGRESSION RESULTS FOR LOG (NUMBER OF LOCATIONS) AS DEPENDENT VARIABLE

	Standardized coefficients
Company	-0.442
Medical college	-0.484*
Hospital	-0.266
Invasive	0.475**
Total number of patents with PS (PCT)	-0.012
Total number of patents with PS (IPO)	-0.038
Multiple R^2	0.287 (F = 3.5***)
Adjusted R^2	0.205

*Significant codes : * p value < 0.1 ** p value < 0.05 *** p value < 0.01.*

Model 2 for number of participants:

Table 4 presents the regression result of the final model 2, as described in equation (ii), where the number of participants is considered as dependent variable. Since the data on number of participants is skewed to the right, we again transformed in this case, the number of participants by taking its logarithmic value. We regressed the independent variables on to the log transformed number of participants. It can be inferred that each of the independent variables considered for the model have significant influence on the dependent variable. The adjusted R-square value was estimated to be 0.561. It is evident that the category of PS whether it is a company or medical college or hospital has negative influences in recruiting the number of participants to conduct a clinical trial. It was also interesting to note that companies had more significant negative influence on number of participants, followed by medical colleges and hospitals. Device category named invasive devices is found to have positive influence on number of participants recruited for clinical trials. Variables related to patent/PCT and patent/IPO gives interesting insights on their influence on determining number of participants in which clinical trials are executed. It can be noted that patent/PCT has positive influence on number of participants. From the conceptual grouping we can interpret that primary sponsors belonging to potential entrant group (having patent/PCT) are executing clinical trials with more number of participants. It can also be noted that patent/IPO has negative influence on number of participants, which from conceptual grouping can be interpreted that primary sponsors belonging to indigenous group (having patent/IPO) execute clinical trials with lesser number of participants than the other two primary sponsor groups viz., incumbent and potential entrant. In case of primary sponsors belonging to incumbent group, (having both patent/PCT and patent/IPO) influence of patent/PCT exhibiting recruitment of more number of participants for clinical trial can be reduced with presence of patent/IPO and thus it becomes advantageous to incumbents to execute clinical trials with appropriate reduced number of participants. Combining the above results we can interpret that though the presence of patent/PCT can exhibit recruitment of more number of participants, presence of patent/IPO shows reduced number of participants required for executing clinical trials. However, this may not have any implication on number of locations.

Results of both the regression models are combined to get valuable insights on decisions pertaining to execution of clinical trials in terms of number of locations for clinical trials execution and number of participants recruited for clinical trials. In case of clinical trials for invasive devices, which require more number of locations and participants, medical colleges may have some control over decisions on number of locations and number of participants while other primary sponsor categories have influence only on number of participants. These insights need further investigations to understand the decisions revolving controls over how the execution of clinical trials must be done.

TABLE 4: REGRESSION RESULTS FOR LOG (NUMBER OF PARTICIPANTS) AS DEPENDENT VARIABLE

	Standardized coefficients
Company	-0.566**
Medical college	-0.461**
Hospital	-0.312**
Invasive	0.382**
Total number of patents with PS(PCT)	0.292**
Total number of patents with PS(IPO)	-0.571**
Multiple R^2	0.607 (F= 13.4***)
Adjusted R^2	0.561

*Significant codes : * p value < 0.1 ** p value < 0.05 *** p value < 0.01.*

V. CONCLUSION

This paper attempted to understand and establish any relationship between the capabilities of a PS to execute clinical trials and their R&D calibre. Conceptual grouping of PS was made to understand variations in number of locations and number of participants involved in clinical trials and crucial decisions from managerial perspectives. Decisions on number of locations and number of participants in each clinical trial involve allocation of resources in form of money, human resources and time. There is also a risk element involved that needs to be managed. A future analysis of device type and category of PS will help, however sample sizes are difficult to find in India, for example the case of stents.

Regression models reveal that decisions on number of locations has some bearing on category of primary sponsor and type of medical device. Also non-invasive devices are clinically tried in lesser number of locations than are invasive devices in India. Decisions on number of participants have some bearing on category of primary sponsor, type of device, number of patent/PCTs and number of patent/IPOs that a primary sponsor has. From the conceptual grouping, it becomes evident that primary sponsors belonging to the potential entrant group who are executing clinical trials with more number of participants, can find it beneficial in terms of reducing the number of participants if they have patent/IPOs. In case of incumbent group, having patent/PCT and patent/IPO, control can be exercised in recruiting number of participants with presence of appropriate number of patent/IPOs. Adjusted R-square value of the first regression model show low value (0.205) whereas for the second regression model it is higher (0.561), implying the need to build a more rigorous models for such analysis and understand the variations in decisions pertaining to number of locations and number of participants involved in any clinical trial process. We assumed that primary sponsors having patent protection in form of patent/PCT or patent/IPO will have more control over both the number or participants and number of locations, thus establishing product leadership and control in the medical device value chain. Surprisingly, primary sponsors of group indigenous (having patent protection only in form of patent/IPO) are found to have significant negative influence on deciding the number of participants recruited for the execution of clinical trials. However, patent protection did not have any significant influence on deciding the number of locations where the clinical trials can be performed. There are many gaps in our exploratory preliminary study. We did not consider the secondary sponsor details in this study. We did not have adequate sample to classify the device type (by name or category such as stent, syringe, pacemaker and such) and the category of primary sponsor, and this might have implications on decisions related to number of participants and locations. Lastly, we could not trace if the specific medical device being tried in clinical trials at India had patents held by the primary or secondary sponsor or the principal investigator for the specific device that is being tried.

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