Impact of the CE mark approval on exit opportunities and valuation for early stage medical device companies

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Abstract

The aim of this thesis was to look at the impact of acquiring the CE marking approval on the outcome of early stage medical device companies, specifically its impact on strategic acquisition opportunities and on valuation.

We gathered data on acquisitions of 237 companies over the past ten years, from April 01, 2002 to March 31, 2011. These data were gathered from various sources, and information on the date of acquisition, enterprise value, funds invested to date, date of incorporation, status and dates of CE and FDA approvals, patent status, type of regulatory clearances (PMA versus 510K), type of sales models (direct versus distributorship), capitalization status and last twelve month stock returns of the acquirer was acquired. These data were then analyzed using basic statistical methods and multivariate linear regression analyses to determine the significance of the CE marking on the outcomes of these companies.

Our results support the claim that the CE mark does significantly improve outcomes for early stage medical device companies, in terms of time to strategic acquisition, which is by far the commonest exit route for these companies. On the other hand, we did not find any statistically significant impact of acquisition of the CE mark on the valuation or valuation multiples of these companies.

These results have potential implications for management of these early stage medical device companies in making strategic decisions and for investors who are concerned about the exit opportunities and valuations, especially as it relates to funds invested. There could also be some policy implications in terms of the effort, duration and cost of getting a CE approval versus that of an FDA approval, which is especially important given the current growing concern about increasingly stringent regulation, rising costs and increasing delays in FDA approvals for medical devices.

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Dedication

To my family,
Rucha, Aayushi, Ranjan, Neela, Urvi, Priyal, Shrikant, Satish, Amar and Punit
for constant encouragement, support and inspiration,
and for providing strong fundamentals, endless opportunities, boundless love and
limitless trust.
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1. Introduction

1.A. Background

The medical device space is rife with examples of small companies with unique technologies creating innovative solutions to a variety of medical problems, at times creating a completely disruptive solution and a completely new market or expanding the market significantly. These companies usually arise out of a market need for a product, go through various steps in the process, from acquiring patents, raising funds, conducting bench-side, animal model and then human studies, getting regulatory clearances, involving physicians, generating publications, creating sales mechanisms, expanding markets, creating a portfolio of products based upon technological, need-based or channel synergies, etc. At some point in their life cycle, based upon a wide variety of factors, these companies may encounter exit opportunities. Most often, the exit opportunity is in the form of a strategic acquirer, who wishes to acquire the early stage company for a variety of reasons. The acquirers’ motivations range from portfolio synergies with existing products, channel synergies, gaining/ maintaining market share, entering a new market/ geography/ segment, patent synergies, scale-up potential, access to a new technology/ platform and others.

Medical devices are regulated by various regulatory agencies such as the Food and Drug Administration (FDA) in the USA, EU competent authorities and the European Medicines Authority (EMEA) in the European Union, the Therapeutic Products Directorate in Canada and the Japanese Ministry of Health and Welfare in Japan. The regulatory process for medical devices, although not usually as protracted as that for drugs, is challenging, and involves significant investment.

In this study, we focused on the European Union (EU) regulatory process for medical devices. The EU regulatory process is governed by three main Medical Device Directives (MDDs). These directives are transposed into the
national rules of each member state, and apart from a few national differences, they provide the roadmap for medical device approval and compliance in the European Union.

All devices that fall within the scope of one of these directives must have the CE marking symbol to be placed on the European market. Most medical devices fall within the scope of the MDD (Medical Devices Directive). Only manufacturers who can demonstrate compliance with the MDD can affix the CE mark on their devices.

CE marking is required in 31 countries in Europe. 27 of those countries are members of the European Union. Three additional European countries, Liechtenstein, Norway and Iceland, are not EU members, but are signatories to the European Economic Area (EEA) treaty. Finally, Switzerland is neither a member of the EU, nor a signatory to the EEA treaty, but it has transposed the Medical Devices Directive into national law and requires CE marking. These 31 countries, plus 3 other candidate EU countries, Croatia, Turkey and Macedonia, recognize the CE marking.

Recently, there are many reports of undue delays in approval of medical devices by the US FDA. Most medical device companies seem to achieve CE marking approval long before the FDA regulatory approval. The importance of thorough screening and establishment of appropriate safety, efficacy and quality standards cannot be over-emphasized. However, excessive delay in the process, coupled with escalating costs may ultimately lead to the stifling of innovation and delayed access to latest technology and cutting-edge medical treatment. The FDA has recently launched initiatives to curtail this growing opinion, and has taken measures to improve the process. However, most medical devices still get approved earlier in the EU than in the US, and many new medical device technologies seem to be available in the EU long before they make their appearance in the USA.
1.B. Research Objectives

In view of the prolonged duration, very high cost and lower approval probability from the FDA, many early stage medical device companies now make strategic decisions to seek EU regulatory approval early in the life cycle, establish a presence in the European markets, generate sales and become cash flow positive before returning to the US to face the prolonged and expensive FDA approval process.

This leads to obvious questions – does acquisition of the CE mark of conformity improve the outcomes of early stage medical device companies? Specifically, does this event trigger an earlier exit opportunity for these companies via a strategic acquisition? Does the valuation asserted by a strategic acquirer improve significantly following acquisition of the CE mark?

This study attempts to answer these questions. We hope to provide the reader of this thesis a sense of the impact of the CE marking on these early stage medical device companies. It is obvious that outcomes and valuations of medical device companies are affected by a multitude of factors and EU approval is only one of a large array of factors. We have attempted to isolate the effects of these other factors in the outcomes using various methods, as we shall discuss going forward.
1.C. Significance and Implications

The results of this study are important, first and foremost, to the entrepreneur, who navigates a sea of tempestuous uncertainties to arrive at decisions determining the early stage company's future, based upon incomplete data and ever-changing realities. Any information, based upon scientific analyses, that can potentially help this executive, who is faced with statistically unfavorable chance of doom, but who also forms the crux of innovation and hope, is bound to be precious.

The management of these early stage companies would also find these data and analyses valuable for making strategic decisions, in the face of multitudes of potential options and an ever looming dearth of funding, as they construct their decision trees, convince their Boards, coax their investors and incentivize their employees.

Investors, including angels, venture capitalists and private equity funds should find this study helpful as they decide on making new investments, consider follow-on rounds, conduct due diligence, advise portfolio companies or seek exit opportunities.

The investment bankers and health care analysts would be equipped with additional tools as they consider providing strategic M&A advice to their clients or as they follow companies and attempt to forecast their outcomes. A significant number of tools applied to this study derive from these sources.

For the strategic acquirers and business development executives of large medical device companies, this study may challenge some of their own biases, providing scientific evidence for or against them. It would also be beneficial for focused effort in the future to identify potential targets and to provide some guidelines for weighting on the valuations for negotiation.
Finally, for the researchers, academics and physicians, I hope reading this thesis will provide you with an insight into the process of taking products from the bench to the bedside via the market and regulatory processes, and serve as an incentive for further innovation and advancement of the field.
2. Hypothesis

The objective of this thesis is to explore the impact of European Union (EU) approval (synonymous with acquisition of the right to affix the “Conformité Européenne” (“European Conformity”) CE mark on the device) on the overall outcomes for early stage medical device companies.

1. Does acquisition of the CE mark facilitate strategic acquisitions for early stage medical device companies?

As medical device companies, in the face of increasingly challenging regulation from the FDA and consequently, increased costs and times to approval, rush for the “low hanging fruit” of EU approval, does this approval significantly improve the positioning of these companies and make them more attractive targets for strategic acquisition?

While strategic acquisition is by no means the only outcome for medical device companies, the vast majority of successful early stage companies do have exits via strategic acquisitions. While some companies have gone on to successful exits via public offerings and some enjoy stellar performance while privately held, the most prevalent and objectively comparable data available were those for the strategic acquisitions.

2. Does acquisition of the CE mark raise the valuation for early stage medical device companies as compared with similar companies acquired without the CE mark, controlling for other factors?

It is not enough to have a successful exit via a strategic acquisition. It is equally important to understand the valuation at exit and the impact of significant events on the valuation of these medical device companies. Does acquisition of the CE mark significantly raise the valuation for these companies and offer more
attractive exit valuations as against those companies that do not have the CE mark approval? Can we reasonably isolate the impact of the CE mark on the valuation and strip off all other considerations, such as size, technology, sales force, sector, acquirer synergies and others?
3. Materials and methods

We collected information on 237 acquisitions in the medical device space between April 1, 2002 and March 31, 2007. We chose target companies exclusively in the medical device sector, which were early stage, had a single product or a single technology based portfolio, were based on a novel technology, had raised external funding prior to being acquired and where detailed information on the deal was publicly available. Complete information on all the factors under consideration was available for 72 companies. These formed the basis for the analyses. The information was collected from multiple databases, including Capital IQ, Windhover, VentureSource, Patsnap, Edgar Online, Hoover’s Online, company websites, SEC filings and analyst reports. We gathered data on the following parameters:

1. Date of transaction
2. Sector
3. Target
4. Acquirer
5. Date of incorporation of target
6. Major product
7. CE marking (Y/N)
8. Date of CE marking approval
9. FDA approval (Y/N)
10. Date of FDA approval
11. Patents (Y/N)
12. Date of issue of primary patent
13. Enterprise valuation of target at acquisition
14. Funds raised by target prior to acquisition
15. Trailing revenue
16. Projected market for the product
17. Single product/ platform technology
18. Type of filing (with FDA) (PMA/ 510(k)/ general controls)
19. Type of sales model (direct/ distributor/ none)
20. Acquirer’s LTM (Last Twelve Months’) stock return
21. Acquirer’s market cap (on the day before acquisition)

1. **Date of transaction:** As mentioned previously, we studied completed strategic acquisitions of early stage medical device companies in the past 10 years’ time period, between April 1, 2002 to March 31, 2011. There were 324 such acquisitions in the time period mentioned. Detailed information on all the above-mentioned parameters was available on 72 of these 324 acquisitions. This subset was used in our quantitative analyses. The time frame was chosen so that it was long enough to generate a practically, economically and statistically robust model, incorporating at least one economic cycle, and short enough to be relevant and recent. We chose to consider the date of closure of the transaction as many transactions were drawn out over long periods of time, and others were not closed or declined.

2. **Sector:** We chose to look exclusively at medical device companies with novel technology. We had many sectors within the medical device space, including cardiovascular, neurology, orthopedics, aesthetic surgery, ophthalmology, otorhinolaryngology, gynecology, general surgery, diabetes, nephrology, respiratory and radiology. The following is a breakup of the various sectors in our sample (Chart 1):
3. **Target**: The targets were chosen to be technology savvy early medical device companies. The reason was that we wanted to study the medical device industry from the viewpoint of the early stage novel, innovative company that has a product/platform that can likely have a large impact on a disease process. We specifically wanted to exclude "me too" manufacturers and manufacturers of generic items such as gloves, test tubes etc. This was done by studying the company's primary product/platform, learning about the technology, understanding the regulatory pathway (PMA, 510(k) or general controls), studying the patents on which the company was the assignee, looking at the target's corporate time line, major events, news and SEC (Securities and Exchange Commission)
filings (10-Ks and 10-Qs) if they exist, or by studying the acquirers’ SEC filings and investor calls to gain a deeper understanding of the factors driving the acquisition and the synergies with the acquirer. Companies with innovative tissue engineered products (especially those of the skin, soft tissues and bone) and minimally invasive devices formed a major fraction of these targets.

4. **Acquirer**: The medical device industry, similar to the pharmaceutical industry, is dominated by an oligopoly – a few large companies dominate the industry and hold the majority of the market share. Not surprisingly, these large medical device companies are usually the acquirers. The following chart demonstrates the major acquirers in our dataset (Chart 2):

**Chart 2: Major acquirers in the medical device industry in our dataset**

<table>
<thead>
<tr>
<th>Acquirer</th>
<th>Number of acquisitions in our dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston Scientific Corp.</td>
<td>7</td>
</tr>
<tr>
<td>Medtronic Inc</td>
<td>5</td>
</tr>
<tr>
<td>Abbott Laboratories Inc</td>
<td>4</td>
</tr>
<tr>
<td>Covidien Ltd</td>
<td>3</td>
</tr>
<tr>
<td>Alcon Inc.</td>
<td>2</td>
</tr>
<tr>
<td>Wright Medical Group</td>
<td>2</td>
</tr>
<tr>
<td>St. Jude Medical Inc</td>
<td>2</td>
</tr>
<tr>
<td>Baxter International Inc</td>
<td>2</td>
</tr>
<tr>
<td>Koninklijke Phillips Electronics NV</td>
<td>2</td>
</tr>
<tr>
<td>NuVasive Inc</td>
<td>2</td>
</tr>
<tr>
<td>Edwards Lifesciences Corp</td>
<td>2</td>
</tr>
<tr>
<td>Kyphon Inc</td>
<td>2</td>
</tr>
</tbody>
</table>
As large companies increasingly become marketing and sales operations, and research and development is increasingly outsourced, these large companies are increasingly looking outward at early stage companies with promising technologies and at academic institutes for disruptive innovations in the medical device field. This, in conjunction with the rapid strides being made in the field of tissue engineering and biomaterials has the effect of pushing up the overall number of M&A deals, especially within the cardiovascular, orthopedic and aesthetic surgery fields. In addition to gaining access to new technology and innovative research, medical device companies also acquire smaller companies for access to product pipeline, new market sector entry, access to IP, consolidation strategy and market share enhancement or maintenance.

1. **Date of incorporation of target**: Studying the impact of regulatory approvals (specifically CE approval, but also to an extent, FDA approval) on the time to exit (TTE) for these companies was one of the primary aims of this study. We used the time since incorporation as a normalizing factor for our measurements. We called this portion of the company’s lifetime, from the time of its approval to its acquisition by a strategic acquirer the approval-exit fraction. This approval-exit fraction allowed us to study and compare the impact of the acquisition in relation to the lifetime of the company.

2. **Major product**: We specifically chose companies with innovative, patented products/technology. A list of the major defining product is part of the database. We observed that minimally invasive devices, cardiovascular devices, orthopedic and spinal implants and tissue engineered products, especially those of the skin, soft tissues and bone form a large majority of the products. These were the most rapidly growing and successful fields in the medical device industry in the past decade. We excluded companies with a wide diversified portfolio and multiple
technologies, as such companies would then have different products at varying stages of development, and this would confound the TTE (time to exit) since the time of multiple approvals and products. Also, it would be difficult to value such a company, as there would be more that one value for the independent variables in the regression model.

3. **CE marking**: We looked at the approval status of the company’s major product. The CE marking denotes compliance with the Medical Device Directives (MDD) of the European Economic region. A company that demonstrates compliance with the relevant MDD (Medical Device Directives) and gets approval to use the CE mark on its device can, with very few further requirements, place its product on the market in 33 European countries.

This information was gained by studying the company’s regulatory filings, news releases and analyst reports.

4. **Date of CE marking approval**: Broadly speaking, the requirements for demonstrating compliance with the MDDs are less stringent than those necessary for demonstrating safety and effectiveness with the US FDA. Thus, in general, the bar for CE approval is lower than that for FDA approval\(^7\). This is also seen in our study, where we find that for most products that have acquired both the CE marking approval and the FDA approval, the CE marking approval date is usually earlier than the date of FDA approval. In our data, we had 53 products that had attained CE approval and 48 that had FDA approval. The average time difference between the two approvals was 9 months, with a standard deviation of 32 months, yielding a t-statistic of 0.29 and a p-value of 0.63. This means that the difference between the FDA and CE approval dates that is observed is not statistically significant at 95% confidence limits. This is probably due to inadequate sample size considering the large variance. We further
calculated that the sample size necessary to make the conclusion based on the above average and standard deviation at 95% confidence limits and for 80% power would be 100 (our sample size was 39 – the number of companies with both CE and FDA approval). The following histogram shows this data in graphical form (Chart 3):

**Chart 3: Interval between CE and FDA approval**

![Histogram showing the interval between CE and FDA approval](chart3)

In addition to being underpowered to draw conclusions based on the data, we also feel that there likely exists a preference bias in this data that is not reflected in the numbers. That is, all companies would not apply for the CE and FDA approval at the same time, in fact, most do not, and hence, to compare the interval between the two approvals may not strictly be representative of all facts. Also, the purpose of this thesis is to look at the time to exit (TTE) after CE approval and its impact on valuation, and not
on the differences in duration between CE and FDA approval times. There are many interesting articles in this regard that the reader of this thesis may be referred to\textsuperscript{6-11}.

5. **FDA approval**: The FDA regulates a broad range of medical devices in the USA\textsuperscript{8,9}, including complicated, high-risk medical devices, e.g. artificial hearts, and relatively simple, low-risk devices, e.g. tongue depressors, as well as devices that fall somewhere in between, e.g. sutures. FDA has authority to regulate medical devices before and after they reach the marketplace. Depending on the device classification\textsuperscript{29}, the FDA requires differing levels of evidence to prove safety and efficacy of the device. In general, devices are classified as class I (lowest risk), class II (intermediate risk) and class III (highest risk), and while some overlap exists, most class I devices need only general controls (GMP – good manufacturing practices – 510(k) exempt), most class II devices are cleared through the 510(k) process (which requires demonstration of substantial equivalence (SE) to an existing device – lower burden of proof), and some class II and most class III devices are approved by the PMA (Pre Market Approval) pathway, which has the maximum burden of proof and usually requires clinical trial data.

The FDA approval is highly coveted by manufacturers as it provides access to the largest and presumably highest paying market in the world for medical devices\textsuperscript{11-14}. Most company executives, medical device analysts, investment bankers and investors of medical device companies who have approvals in both the US and EU markets model 2/3\textsuperscript{rd} of their earnings from US sales and 1/3\textsuperscript{rd} from rest of world sales. While this convention may vary across companies, type of products, practice trends, etc., on average, the convention holds true. This underscores the importance of FDA approval to the overall company strategy. Even those companies that target early CE approval do so for constraints of time and
cost, and usually do plan to file for US FDA approval at a later stage in their life cycle. In fact, conversations with entrepreneurs, angels and venture investors who have used this strategy seem to imply that the primary purpose of early CE approval is to advance the company to revenue and cash flow positive status. Generating additional data from post market surveillance for submission to FDA is an additional motive for these companies.

In the recent years, there has been increasing dissatisfaction with the FDA due to prolonged time and associated costs involved in getting approvals for medical devices\textsuperscript{11}. There is no doubt that we need to protect the patients from undue harm by better weighing the efficacy and safety of new medical devices. However, we also need to consider whether overzealous regulation is stifling innovation and delaying access to new technology and next generation products.

6. Date of FDA approval: This data was available from the FDA archives. As mentioned previously, for companies with both CE and FDA approvals, FDA approvals happened on average after CE approvals. However, some companies that had FDA approval did not have CE approvals. These companies seemed to have focused exclusively on the US markets and not on the EU market. On the other hand, in case of companies with a CE approval but no FDA approval, most seemed to be in the process of obtaining the FDA approval. We also looked at the IDE (Investigational drug exemption – this status allows the device to be used in the US for clinical trial purpose under the supervision of a clinical investigator with the approval of the hospital/ institution’s review board (IRB approval)). It was found that in almost all cases where the product had a CE marking approval, and was not yet FDA approved, the product had an IDE (Institutional Device Exemption) status and was in trials in the United States, or in few cases, had been reviewed and denied approval.
7. **Patents:** Intellectual property (IP) protection is extremely important for early stage technology based medical device companies\textsuperscript{16}\textsuperscript{,17} as a significant amount of capital (usually in tens of millions) is invested over a prolonged period of time (timeline – 3 to 7 years on average), with lower odds of success than in many other ventures. Although not impossible, it is very difficult to raise funding from sophisticated investors for a medical device venture without having filed for patent protection on the idea/product/device. In fact, this fact is confirmed from our data, where we found that all 72 companies in our study had at least one and generally many patents around the idea. We further studied the patents held by the companies to determine the most fundamental patent covering the device, and used the date of issue of this fundamental patent as the guiding date for our analyses.

We used Patsnap\textsuperscript{©,25} extensively, which is a patent database that includes data on both issued patents and applications from 1876 onward on US and international patents. It also features extensive browsing, sort and filter options, patent family searches, "more like this" information and assignee changes (which incidentally was very helpful in our work). Additionally, we used information from the United States Patent and Trademark Office (USPTO)\textsuperscript{26}, FreePatentsOnline, Google Patents\textsuperscript{27}, Bios Patent Lens and Scopus. The USPTO is a free service run by the US patent and trademark office, which gives information on application status and assignee changes, but has complex syntax, requires a TIFF viewer for images and does not support portable document format (PDF). Google Patents came up with some errors and the assignee changes were not found to be reliable. Scopus is an excellent subscription only database that has excellent search and extended search capabilities and is the most versatile format to apply filters and generate additional information on patents.
8. **Date of issue of primary patent:** From the above databases, we studied the various patents applied for the products. Typically, most companies had multiple patent claims around a single product (product claim) or process (process claim). We chose to pick the broadest version of the most independent claim made relating to a product or process. There were instances when more than one patent could be claimed as being fundamental to the product under consideration, and under those conditions, we chose to pick the earlier patent. We reviewed many patent claims and observe that some companies as a strategy built out a large patent estate around a product/technology, while others were more narrowly focused on their particular embodiments of the technology, as they related to the product under development, probably because broad claims were unavailable because of significant prior art.

Some academic institutions, individuals and companies typically tend to build huge portfolios of patent claims, and in general, this is the strategy that is advocated by patent lawyers and academicians. Increasingly, we found large companies following the same strategy. On the other hand, some entrepreneurs and company management want to protect their own device and do not worry much about protecting the overall space.

For companies that did not hold either a CE mark approval or an FDA approval, the date of filing of the most fundamental patent protecting the technology/process was taken as the significant event in our analyses.

9. **Enterprise value of the target at acquisition**\(^{13,14}\): Enterprise value is the value of the entire firm, including the value to the equity holders and the debt holders of the company (Enterprise value = Equity value + Value of all outstanding debt). It represents the true comprehensive value of the firm and is usually used by the acquirer in valuing the firm. Financial
theory explains how the relative contribution of equity and debt contribute to the overall financial risk of the firm. Broadly, the higher the amount of debt, the higher is the amount of interest and principal outflow for the firm (debt holders have priority on the cash flows of the firm) and the less the ultimate payout to the equity holders, thereby making the firm increasingly risky to the equity holders. Also, increasing debt brings with itself all the associated costs of financial distress – even if the firm does not actually go into actual bankruptcy. This can be explained from two perspectives.

First, for a firm with high levels of debt, the interest and capital repayments may be so significant and the resultant debt obligation (interest and principal repayable in a period) to cash flow ratios so low that the firm, operating on thin margins, may not take on good positive net present value (NPV) projects that they could otherwise have taken up. Additionally, the firm is unable to respond to business cycle downturns and economic shocks that it could otherwise have easily absorbed. Finally, very high debt levels can induce the equity holders to make poor management decisions because of the inherent risk imbalance (i.e. gambling on debt holders’ capital). On the other hand, an all-equity firm loses out on the interest tax shield provided by debt, as well as can induce poor management decisions (agency problems) due to stock piling of huge levels of cash reserves (excess cash without any obligation to make payouts and overly optimistic forecasting of the potential benefit of new projects). Thus, companies must strive to achieve and maintain an optimum capital structure (mix of debt and equity).

Most early stage medical device companies are all-equity firms. Debt capacity is restricted because of negative cash flows. These firms often tend to be so risky that even the equity investments are often structured as convertible debt instruments. Also, any debt issued by such companies
tends to be in the form of convertible debt to allow the investors access to the potential upside of investing in the risky debt.

Acquisitions can either be asset acquisitions or stock acquisitions. In an asset acquisition, the acquirer chooses the type and amounts of assets of the firm that it wishes to purchase. Typically, most acquisitions of medical device companies involve stock acquisitions with change of control provisions. Asset purchase acquisitions tend to have greater tax benefits for the acquirer. Stock acquisitions, on the other hand, have fewer tax benefits.

We used the enterprise value of the firm as the factor for our analyses. For those firms where the deal involved less than complete asset buyouts, we used the implied enterprise value of the firm, calculated by looking at the company's outstanding debt liability in case of equity buyouts and from looking at the implied value of the assets not purchased, and adding them back to the price paid in cases of partial asset purchases. Capital IQ, Windhover and Hoovers online were excellent resources that were helpful in our analyses.

Most of the acquisitions in our dataset carried enterprise values between $10 and $1000 million, with a few outliers. The average enterprise value was $209 million, median value $80 million. The following chart illustrates a histogram of the data on enterprise values in the sample:
10. **Funds raised by target prior to the acquisition:** We gathered this information from Capital IQ, Windhover, VertureSource and VentureX databases. Despite using multiple databases, this parameter was not always available, and dearth of this information was the number one cause of dropouts from our dataset to reach the sample size of 72 companies.

We used this data to normalize the enterprise value of the companies to give the return on funds invested ratio. This is because enterprise value represents an all-inclusive number that takes into account factors such as firm size, potential market size, sector, pre-acquisition revenues, acquirer related factors such as size of acquirer, acquirer synergies in terms of technology, sales force, IP, and many other factors. We submit that the amount of funds invested may serve as a good normalizing factor to collectively combine the above factors. This is based on the fact that most
investors in these early stage companies would be sophisticated venture investors or private equity funds, who would typically have in-depth understanding of the above factors.

The average investment in our dataset was $53 million, and the median investment was $47 million. Following is a histogram of funds invested in our dataset (Chart 5):

![Chart 5: Histogram of Funds Invested](image)

Return on funds invested is a good measure of outcomes in financial analysis. We look at this measure (Enterprise value/ funds invested) as a return measure on all previous investment into the company made by investors. This is, in broad terms, the return that the venture investors made on these companies. The returns had a range of 0.02X to 37.5X of funds invested, with an average of 6.6X and a median of 4.7X. Following is a histogram representing the entire dataset (Chart 6):
Speaking very broadly, one can say based on the above data that venture investors in this period invested on average $53 million in a medical device company that was successfully acquired, and the average return on investment was 6.6X. Of course, these are averages of a relatively small dataset of companies whose information was available and where the company was based on a novel technology and had a successful exit via strategic acquisition.

11. Trailing revenues: Past performance can be a valid predictor of future potential. This was the principle underlying the use of this parameter for normalizing the enterprise value.

Revenue Multiple (Enterprise value/ Trailing Revenue ratio) is also widely used in the industry by business development executives, analysts and bankers to value companies. This is a good multiple for companies with
negative earnings. However, revenues can be manipulated, and an awareness of the revenue recognition practices is important. A detailed revelation of revenue recognition practices was not available for companies in our dataset. Additionally, some companies in our dataset were pre revenue, which made the Revenue multiple unusable for those cases.

12. **Projected market:** Projected market for a product may be another important factor for normalizing the enterprise value. We call this the market fraction (Enterprise value/ Project market). It represents the fraction of the total potential total market for the product that the acquirer paid for the company. We determined the projected market for a particular product from news announcements of the acquisition, the acquirers’ SEC filings (usually 10-K or 10-Q) or from analyst reports. We feel that the acquirers’ projections of market size were probably the most useful in this regard.

We found that this data was often inconsistent. This may be due to the fact that the projected market for a product is ultimately a forecast, which may be a moving target. Also, its definition may be different under differing circumstances, resulting in a referral bias. It is not always possible to get this data at the time of the acquisition, and this may result in a temporal bias. The acquirer’s management often refers to the synergistic opportunity created through the acquisition of the target, which may lead to an inflation of the true market of the product of the target. Finally, the phenomenon of over-optimism on the part of the acquirer that results in the acquirer often over paying for a target is well known (acquirer exuberance); and this phenomenon may also be passed over onto the projections for the target, including its products’ projected market.
13. **Single product/ portfolio:** Some companies are completely focused on the development and marketing of a single product/ technology in a single niche area. These are defined as single product companies. Other companies, on the other hand, are very focused on developing a portfolio of products based on the technology/ platform and/ or on extending the use of the same to other therapeutic areas. These were classified as portfolio companies\textsuperscript{15,16}.

In order to keep the analyses simple, and to encourage inclusion of more early-stage companies in our dataset, we intentionally excluded companies with multiple unique technologies/ platforms/ products as these tended to be more mature companies and the variables would soon get very complex.

This information was found by analyzing the company’s product offerings, IP applications, news releases, analyst reports and SEC filings. It may be an important factor in the valuation process. We hypothesize that portfolio companies should have higher enterprise values at exit versus single product companies.

14. **Regulatory filing (PMA/ 510(k)/ 510(k) exempt general controls):**
Depending on the complexity of the product and its potential risk to the patient, and the availability of pre-existing proven substantially equivalent products, the type of filing for approval with the FDA is different. High-risk class III devices, with no substantially equivalent prior products need to go through the longer and more rigorous PMA (Pre Market Approval) process. Lower risk class II products or those with proven existing substantially equivalent products undergo the 510(k) clearance process, where the burden of proof is lower than that of the PMA process. The lowest risk class I devices may be deemed 510(k) exempt, and they need to demonstrate general controls (such as compliance with Good
Manufacturing Practice – GMP and at times, Good Clinical and/or Good Laboratory Practice – GCP and/or GLP respectively) for approval. The burden of proof is lowest in these cases, and the approval process relatively easier.

The enterprise value of the company depends on the regulatory filing and burden of proof for the product, with a higher burden of proof such as the PMA being associated with higher return, greater competitive advantage and higher barrier to entry, and hence, higher valuation. On the other hand, a higher burden of proof also means higher uncertainty, longer process and higher costs, and hence, higher overall risk. This variable is almost always a major consideration in the valuation process by analysts, bankers and business development executives.

15. Type of sales force (direct/ distributor/ none): The type of sales force model is an important factor that determines companies’ valuations. Determining the type of sales force to use for the product is always a very difficult challenge for an early stage company. Direct sales force would seem ideal in that it would entail a focused specialized group of individuals who have a deep understanding of the product, and who would target the physicians and customers specifically for the company’s product. However, the direct sales force is expensive to develop and maintain, and from a small company’s viewpoint, may not have enough coverage to target a broad enough audience.

A distributor’s sales force, on the other hand, relies on the existing sales network of the distributor to market the product. The sales force is not specifically trained in the intricacies of the product, nor is it their only agenda to sell the company’s product. However, distributors’ sales forces are broadly available, are relatively inexpensive and have an existing channel influence.
From the acquirers' viewpoint, most acquirers have established sales forces and sales force synergy is one of the major synergies that strategic acquirers in the medical device space leverage upon. However, except for a few circumstances, the acquirers' sales force is not a specialist on the target's product. Also, existing distributor sales force implies an ongoing contract with the distributor for owning distributorship of the product, which may be a challenge for a strategic acquirer who may wish to integrate the products into its own distribution channel to leverage on the synergy value.

On average, it can be said that a company with a direct sales force should be able to command higher valuation multiples than one that uses a distributor's sales force or one that does not have any sales force. In fact, a good sales force for a product may be a major strategic advantage for an early stage company, especially one where the product is a highly specialized one and whose sales are dependent on the sales forces' relationships with a few key stakeholders/physicians/key opinion leaders.

We gained information on the type of sales force from the company websites, product news, analyst reports and acquirers' SEC filings. Some very early stage, pre-revenue companies had no sales force. A hybrid construct, with a direct sales network in the home country (US or Israel) and a distributor network in other parts of the world, especially in the EU, was a common structure. This may be due to the existing strong distributor relationships and the health care systems in the different countries.

16. Acquirer's LTM (Last Twelve Months') stock returns (on the day prior to the acquisition): This variable was added on the basis of the argument
that acquirers who have had a significant rise in stock price over the past
twelve months have relatively higher amounts of relatively cheap financing
in the form of inflated equity capital to invest and hence may offer higher
valuation multiples than other companies who may need to raise such
capital from the capital markets by issuing new debt or equity at a higher
cost.

This information was available through Capital IQ M&A database and
through Windhover. We observed that in our sample, the acquirers' LTM
stock returns on average were 2.26% and the median was 0%. Following
is a histogram of the acquirers' LTM stock return on the day prior to the
acquisition (Chart 7):

Chart 7: Histogram of Acquirers' Last Twelve Months Stock Return

17. Acquirers’ total capitalization (on the day prior to the acquisition): The
assumption here was that larger acquirers, with higher capitalization
should have better resources, access to bigger markets, larger sales
force, more rapid penetration of the product, more efficient management
through higher synergies with existing resources and better execution to enable them to extract greater value from the product and thus pay higher multiples.

This information was also available through Capital IQ M&A database and through Windhover. We observed that in our sample, the acquirers' total capitalization on average was $14.35 billion and the median was $5 billion. Following is a histogram of the same on the day prior to the acquisition (Chart 8):

**Chart 8: Histogram of Acquirers' Market Capitalization Day Before Acquisition**

![Histogram chart](image-url)
Analyses:

For exit opportunities post CE mark approval:

From the perspective of time to exit (TTE), we studied the time from various events to the date of completion of the acquisition for these companies. In particular, we looked at the time to exit from the date of incorporation, the date of issue of first relevant patent, date of acquiring the CE mark and the date of acquiring the FDA approval. For companies that had both an FDA approval and a CE approval for the chief product, we looked at the time to acquisition since each approval separately, i.e., they were included in both the subgroups for analyses and analyzed from the times of respective approvals to exit. We also looked at the time from issue of the relevant patents to exit for companies with and without approvals, and at the time from incorporation. To further normalize the data, we looked at the ratio of time since approval (CE/FDA) to time from incorporation (the post approval fraction) and this ratio gave us a much better approximation of the normal distribution. Time from incorporation to exit (approval-exit fraction) was taken as the normalizing parameter since this represents the entire life span of the company as an independent entity. The ratio represents the fraction of that life span that can be attributed to the time between CE marking to exit. We looked at the significance of this post approval fraction to determine the significance of the event on the lifecycle of the firm, specifically with respect to exit opportunities. We looked at the average time to exit (TTE) since these various events, and the variation around the means, and used appropriate statistical measures (t-test) to compare these means, medians and variances.
For impact on valuation post CE mark approval:

Valuation of a company depends on multiple factors, and we first used a simple t-test to see if the valuations for companies with only CE marking approval were significantly different from those for companies with FDA approval only, for companies with both FDA and CE approval and for companies with neither FDA nor CE approval. We studied the impact in relation to the Enterprise value, and then added various normalizing parameters to attempt to normalize for the various other factors involved in the process. In this regard, we studied the impact of the CE marking approval on the Enterprise value/ Funds Invested (ROI - return on investment), Enterprise value/ Trailing revenues (Revenue Multiple), Enterprise value/ Projected market (Market Fraction) using univariate linear regression models.

We also ran multivariate linear regression models to generate an overall model incorporating the various parameters that are commonly used as inputs for valuing these companies and tried to come up with a predictive model. We looked at the predictability of the models and also at the coefficients for each parameter and its significance within the model.

We ran multiple versions of the model, using certain parameters and omitting others to come up with the best predictive mathematical model. In its most basic form, the model looks like the following:
Enterprise value/ Funds invested = \( \alpha \)

+ \( \beta_1 \) * CE marking approval (BIN)
+ \( \beta_2 \) * FDA approval (BIN)
+ \( \beta_3 \) * Trailing 12 months' revenue
+ \( \beta_4 \) * Projected markets
+ \( \beta_5 \) * Single product/ Portfolio (BIN)
+ \( \beta_6 \) * Sales force (Direct/ Distributor/ None)
+ \( \beta_7 \) * Type of filing (PMA/ 510(k) (BIN)
+ \( \beta_8 \) * Acquirer's LTM stock returns
+ \( \beta_9 \) * Acquirer's Market Capitalization
+ \( \epsilon \)
4. Results:

4.A. Impact of CE marking approval on exit opportunities:

Our hypothesis was that the CE marking approval should decrease the TTE and the approval-exit fraction. Our analyses suggest that companies with CE mark approval do have statistically shorter times to exit (p value = 0.0005) when compared against companies that do not have any approvals. Thus, we can reject the null hypothesis that the CE marking approval does not impact the TTE for early stage medical device companies within 95% confidence interval and accept the alternative hypothesis that the TTE is significantly shortened.

Additionally, we found that companies with both CE and FDA approval had even shorter TTEs than did companies with only CE marking approval and this difference was also statistically significant (p value = 0.005).

Finally, companies with only FDA approval and no CE marking approval were found to have shorter TTEs than companies with only CE marking approval (p value = 0.03).

For the approval-exit fractions (TTE since approval/ TTE since incorporation), our results indicate a similar trend, with companies with both CE and FDA approvals having approval-exit fractions smaller than those with only CE approvals (p value = 0.02), and companies with CE approvals only having shorter approval-exit fractions than those with no approvals ((p value = 0.0008). There was no statistically significant difference in the approval-exit fractions of companies with CE approval only and those with FDA approvals only (p value = 0.09).

The following charts summarize the results and their interpretations (Chart 9 and Chart 10):
Chart 9: Summary of results on TTE (Time to Exit)

<table>
<thead>
<tr>
<th></th>
<th>TTE compared with only CE approved company</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p value</td>
<td>H0 rejected - Yes/ No</td>
</tr>
<tr>
<td>Only FDA approved</td>
<td>0.0314</td>
<td>Yes</td>
</tr>
<tr>
<td>CE + FDA approved</td>
<td>0.0005</td>
<td>Yes</td>
</tr>
<tr>
<td>No approval</td>
<td>0.0005</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Chart 10: Summary of results on Approval/ Exit Ratio

<table>
<thead>
<tr>
<th></th>
<th>Approval/Exit ratio compared with only CE approved company</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p value</td>
<td>H0 rejected - Yes/ No</td>
</tr>
<tr>
<td>Only FDA approved</td>
<td>0.0921</td>
<td>No</td>
</tr>
<tr>
<td>CE + FDA approved</td>
<td>0.0235</td>
<td>Yes</td>
</tr>
<tr>
<td>No approval</td>
<td>0.0008</td>
<td>Yes</td>
</tr>
</tbody>
</table>
4.B. Impact of CE marking approval on valuation:

**Impact on Enterprise value:** From the viewpoint of valuation, our hypothesis was that companies with CE marking approval should have higher valuations than those without any approval. Our results indicate that we cannot reject the null hypothesis that there is no statistically significant difference in the enterprise value of companies with CE mark approval as against those with no approval \( (p \text{ value} = 0.44) \). Additionally, we could not find any statistically significant difference in the valuations of companies with both CE and FDA approvals \( (p \text{ value} = 0.2553) \) or of companies with only FDA approval \( (p \text{ value} = 0.34) \) against the valuations of companies with only CE marking approval. This is summarized in the chart below (Chart 11):

**Chart 11: Summary of results of impact on Enterprise Value**

<table>
<thead>
<tr>
<th>Enterprise value (EV)</th>
<th>EV compared with only CE approved company</th>
<th>H0 rejected - Yes/ No</th>
<th>TTE shorter/ longer with CE approval only</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only FDA approved</td>
<td>0.3433</td>
<td>No</td>
<td>-</td>
<td>EV is not significantly different for companies with CE approval only as against companies with only FDA approval, companies with both CE and FDA approval and companies with no approval</td>
</tr>
<tr>
<td>CE + FDA approved</td>
<td>0.2553</td>
<td>No</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>No approval</td>
<td>0.4377</td>
<td>No</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Impact on Return on Investment (= Enterprise Value/ Funds Invested):

There was no statistically significant difference in the return on investment for companies with CE mark approval only as against companies with FDA approval (p value = 0.1396), companies with both CE and FDA approval (p value = 0.0761) and companies with no approval (p value = 0.4123).

Chart 12 below summarizes these findings:

**Chart 12: Summary of results of impact on EV/FI (ROI)
(Enterprise Value/ Funds Invested = Return on Investment)**

<table>
<thead>
<tr>
<th>Enterprise value/ Funds Invested</th>
<th>EV/FI compared with only CE approved company</th>
<th>TTE shorter/ longer with CE approval only</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only FDA approved</td>
<td>p value</td>
<td>H0 rejected - Yes/ No</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.1396</td>
<td>No</td>
<td>EV/FI is not significantly different for companies with CE approval only as against companies with only FDA approval, companies with both CE and FDA approval and companies with no approval</td>
</tr>
<tr>
<td>CE + FDA approved</td>
<td>0.0761</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>No approval</td>
<td>0.4123</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Impact on Revenue Multiple (Enterprise Value/Revenue): There was no statistically significant difference in the revenue multiple for companies with CE mark approval only as against companies with FDA approval (p value = 0.1718), companies with both CE and FDA approval (p value = 0.4665) and companies with no approval (p value = 0.1683). Chart 13 summarizes these findings.

Chart 13: Summary of results of impact on EV/Revenue (Revenue multiple)

<table>
<thead>
<tr>
<th>Enterprise value/Revenue (EV/Rev)</th>
<th>EV/Rev compared with only CE approved company</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p value</td>
<td>H0 rejected - Yes/ No</td>
</tr>
<tr>
<td>Only FDA approved</td>
<td>0.1718</td>
<td>No</td>
</tr>
<tr>
<td>CE + FDA approved</td>
<td>0.4665</td>
<td>No</td>
</tr>
<tr>
<td>No approval</td>
<td>0.1683</td>
<td>No</td>
</tr>
</tbody>
</table>

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Impact on Market Fraction (Enterprise value/Projected market): There was no statistically significant difference in the market fraction for companies with CE mark approval only as against companies with FDA approval (p value = 0.2251), companies with both CE and FDA approval (p value = 0.4240) and companies with no approval (p value = 0.3833). Chart 14 summarizes these findings:

**Chart 14: Impact on Market Fraction (EV/Projected Market)**

<table>
<thead>
<tr>
<th>Enterprise value/Market (EV/Mar)</th>
<th>EV/Mar compared with only CE approved company</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only FDA approved</td>
<td>p value 0.2251</td>
<td>H0 rejected - Yes/ No</td>
</tr>
<tr>
<td>CE + FDA approved</td>
<td>p value 0.4240</td>
<td>H0 rejected - Yes/ No</td>
</tr>
<tr>
<td>No approval</td>
<td>p value 0.3833</td>
<td>H0 rejected - Yes/ No</td>
</tr>
</tbody>
</table>
Linear regression models (Univariate): We further used a linear regression model by regressing each of the above parameters against the CE approval status of the company. We found no single model that explained the data more than 10% of the times and we never observed any significance in the F score or in the p value of the coefficient. Chart 15 summarizes the result of our univariate linear regression models:

Chart 15: Summary of results of univariate linear regression

<table>
<thead>
<tr>
<th>Regression parameters (Y vs. X)</th>
<th>EV vs. CE</th>
<th>EV/FI vs. CE</th>
<th>EV/REV vs. CE</th>
<th>EV/Markets vs. CE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R Squared</strong></td>
<td>0.00</td>
<td>0.07</td>
<td>0.10</td>
<td>0.00</td>
</tr>
<tr>
<td><strong>Adjusted R Squared</strong></td>
<td>-0.01</td>
<td>0.05</td>
<td>0.09</td>
<td>-0.01</td>
</tr>
<tr>
<td><strong>Significance F</strong></td>
<td>0.92</td>
<td>0.05</td>
<td>0.01</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Coef (CE marking)</strong></td>
<td>-8.47</td>
<td>-5.29</td>
<td>0.00</td>
<td>-0.01</td>
</tr>
<tr>
<td><strong>p value of Coef</strong></td>
<td>0.92</td>
<td>0.05</td>
<td>0.00</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Multivariate regression model: Finally, we used a multivariate linear regression model, incorporating all the parameters that could be used in the evaluation model described in the materials section. A multivariate regression model allows one to tie a number of independent variables and their relationship to a dependent variable, in this case the EV/Funds Invested or return on funds invested ratio. Our multivariate regression was of the type:

\[
\text{Enterprise value/ Funds invested} = \alpha + \beta_1 \times \text{CE marking approval (BIN)} + \beta_2 \times \text{FDA approval (BIN)} + \beta_3 \times \text{Trailing 12 months' revenue} + \beta_4 \times \text{Projected markets} + \beta_5 \times \text{Single product/ Portfolio (BIN)} + \beta_6 \times \text{Sales force (Direct/ Distributor/ None)} + \beta_7 \times \text{Type of filing (PMA/ 510(k) (BIN)} + \beta_8 \times \text{Acquirer's LTM stock returns} + \beta_9 \times \text{Acquirer's Market Capitalization} + \epsilon
\]

The output of this multivariate regression was not significant (as evidenced by an R-squared value of 20%, an adjusted R-squared value of 3%, a value of significance of F statistic of 0.33 and p values of all the coefficients being > 0.05). This implies that the regression model produced can explain only 3% of the variability (adjusted R-squared score) in the dependent variable (EV/Funds invested ratio) using the independent variables (shown in the model above). Additionally, a significance value of the F statistic of 0.33 means that we cannot reject the null hypothesis at the 95% significance level that the intergroup variability in the data is the same as the intra-group variability. This implies that the model generated cannot be used to make predictions, nor can it be used to determine the significance of any of the independent variables.
We ran multiple such models, and regressed different parameters against EV, EV/ Funds Invested, EV/ Revenues and EV/Market as the dependent variables and differing combinations of the dependent variables. However, in all cases we did not reach anywhere close to the R-squared value of greater than 55, nor did we get a value of significance of F of less than 0.05. We conclude that it was not possible in our study to generate a reasonable multivariate linear regression model with the most logical independent variables and to generate a
mathematically sound model that can predict the valuation of an early stage medical device company with high degree of precision.
4.C. Summary of results:

Results with regard to impact on TTE (Time to approval):

Our analyses suggest that companies with CE mark approval do have statistically shorter times to exit \((p \text{ value } = 0.0005)\) when compared against companies that do not have any approvals.

Additionally, companies with both CE and FDA approval had even shorter TTEs than did companies with only CE marking approval and this difference was also statistically significant \((p \text{ value } = 0.005)\). Finally, companies with only FDA approval and no CE marking approval were found to have shorter TTEs than companies with only CE marking approval \((p \text{ value } = 0.03)\).

For the approval-exit fractions (TTE since approval/ TTE since incorporation), our results indicate a similar trend, with companies with both CE and FDA approvals having approval-exit fractions smaller than those with only CE approvals \((p \text{ value } = 0.02)\), and companies with CE approvals only having shorter approval-exit fractions than those with no approvals \((p \text{ value } = 0.0008)\). There was no statistically significant difference in the approval-exit fractions of companies with CE approval only and those with FDA approvals only \((p \text{ value } = 0.09)\).

Results with regard to impact on valuation:

There was no statistically significant difference in the enterprise value for companies with CE mark approval only as against companies with FDA approval \((p \text{ value } = 0.3433)\), companies with both CE and FDA approval \((p \text{ value } = 0.2553)\) and companies with no approval \((p \text{ value } = 0.4377)\).

There was no statistically significant difference in the enterprise value/ funds invested ratio (return on funds invested), enterprise value/ revenues ratio
(revenue multiple) or enterprise value/ projected markets (market share fraction) ratio for companies with CE mark approval only as against companies with FDA approval, companies with both CE and FDA approval and companies with no approval.

Our simple linear regression model involving regressing each of the above (EV, EV/ Funds invested, EV/ Revenues, EV/ Project market) against the CE approval status of the company. We found no single model that explained the data more that 10% of the times and we never achieved any significance in the F score or in the p value of the coefficient.

Finally, our multivariate linear regression model, incorporating CE marking approval (BIN), FDA approval (BIN), Trailing 12 months' revenue, Projected markets, Single product/ Portfolio (BIN), Sales force (Direct/ Distributor or None) (BIN), Type of filing (PMA/ 510(k) (BIN), Acquirer’s LTM stock returns, Acquirer’s Market Capitalization, also did not achieve statistical significance (as evidenced by an R-squared value of 20%, an adjusted R-squared value of 3%, a value of significance of F statistic of 0.33 and p values of all the coefficients being > 0.05). This implies that the model generated cannot be used to make predictions, nor can it be used to determine the significance of any of the independent variables.

Our further attempts including regressing different parameters against EV, EV/ Funds Invested, EV/ Revenues and EV/Market as the dependent variables and differing combinations of the dependent variables did not reach anywhere close to the R-squared value of greater than 55, nor did we get a value of significance of F of less than 0.05. We conclude that it was not possible in our study to generate a reasonable multivariate linear regression model with the most logical independent variables and to generate a mathematically sound model that can predict the valuation of an early stage medical device company with high degree of precision.
5. Discussion:

5.A. Impact on exit opportunities:

The aim of this thesis was to determine the impact of achieving the CE approval mark on the exit opportunities and valuation of early stage medical device companies. Our hypotheses were that the time to acquisition should be shortened and the valuation higher than that without the CE marking approval.

The results confirm our hypotheses on the exit opportunities front. The time to exit is significantly improved by a CE marking approval (additionally, our results tell us that CE+FDA approval and FDA approval only lead to even faster exits in that order). These results confirm our logical deduction that the regulatory approvals are major value inflection points in the company’s life cycle. The FDA approval seems to be more valuable in this regard than the CE approval, which again makes logical sense considering that the US is a much bigger market, reimbursements tend to be higher and FDA approval is more difficult to achieve. However, for early stage companies on the margin, who are trying to conserve cash, for whom reaching the market faster could make the difference between survival and demise, who wish to achieve cash flow positive status as soon as possible, and who want to be early to market, the going after the CE marking approval does make strategic sense. It does seem to make the investors more confident and does seem to attract the strategic acquirer.

It may be argued that time to exit is relative, in that all companies may not seek to be acquired as soon as possible. Many early stage companies may seek to optimize their market position before considering exit or may wish to continue to operate independently within their own niche or may decide to expand their portfolio and become a diversified large device company, to eventually position themselves for competition with the current oligopoly in the industry. Hence, time to exit may not be an accurate representation of the outcome of such a company.
However, more than 95% of companies in this space do exit via acquisition. Also, seeking an exit is not necessarily the only way a company gets acquired. There exists a complex interplay of factors including management capability, patent estate, market and customer dynamics, investor timelines, general economic conditions, acquirers’ deal-making capabilities, etc. that determine an early stage company’s exit. Hence, once a company is sufficiently on the radar for an acquisition, the relative weighting of each of these factors on the eventual outcome is very difficult to determine. Hence, we make the simplistic assumption that exits happen as soon as possible contingent upon being an attractive target. This is of course not true. There are definite examples of this within our own dataset. However, these tend to be the exception rather than the rule. As we look back at retrospective data and make statistical associations, there arises the necessity to make simplifying assumptions so that we may reach a state of the world “on average”, “within 95% confidence limits”. In fact, the absolute basis of data analysis, which attempts to use past data to forecast future trends is based on the assumption that those trends would hold going forward. This may partially be circumvented, and the assumption strengthened by dividing the data set into an experimental set on which to establish the trends, and another test set on which to test the same. These trends may be utilized for lack of availability of more robust ways of experimentation, as guiding principles for decisions that still need to be made under incomplete data and uncertainty of outcomes.

Based on the above arguments, we can conclude that on average, for most early-stage medical device companies, acquisition of the CE mark approval does provide better exit opportunities through strategic acquisition.
5.B. Impact on valuation:

As in our discussion on TTE, it is appropriate to reiterate here that regulatory approval of a medical device is a major value inflection step in the life cycle of a medical device company. It stands to reason that achieving CE marking approval should raise the valuation of a company significantly over one that does not have any approval. Extending the same argument, it stands to reason that since FDA approval provides access to the largest market segment, its value should be even higher.

However, in our results, we are unable to find any significant association of either approval on the company's valuation. This brings to light some of the arguments that we made in the previous section regarding the significance of statistical associations based on historical data.

Valuation is an immensely complex exercise. At its very basic, it is simply a present value of current and forecasted cash flows, discounted back at an appropriate risk-adjusted discount rate (also known as the adjusted present value or APV method). Moving deeper into valuation theory, we realize that there are multiple assumptions built into these cash flow forecasts and into the discount rates, which require deep understanding of the fundamentals of the business and the technology. In the case of medical device companies, there is usually a portfolio of products at different stages of development that face very different levels of risk and uncertainty. Additionally, the risk of a company varies significantly, depending on the stage of development of its chief technology. The risk is very high in the early proof-of-concept stage, and decreases exponentially as the company moves forward through the animal testing, pilot and pivotal trails, approval, marketing, reimbursement, acceptance and finally, the ultimate stage of the technology/device attaining the coveted status of being "standard of care." The risk at each of these levels is very different, and this has to be reflected in the discount rate applied to the projections of the cash flows. In fact, traditionally,
venture capital investors have incorporated terms such as convertible preferred or participating preferred stock that look like a combination debt and equity. A significant amount of financing for many of these firms, even in the more advanced stages of their life cycle tends to be convertible debt. This reflects the risk of the investment, and a way for the companies to issue debt at better terms than they otherwise could through straight debt instruments, because of the added value of the upside option of converting to stock, and for the investor, a stock with downside protection, through the debt instrument. Another major source of risk today comes from the uncertainty surrounding reimbursement – policy changes requiring major overhaul of payment systems in the US, the major market, and economic downturns in many advanced nations, making it easier to argue for lower cost alternatives and also to deny/ration treatment based upon a range of factors, make it important for the company to think seriously about the pharmaco-economic challenges surrounding their device offerings. Additional risk factors include technological risk, regulatory risk, clinical risk, biological risk, end customer acceptance risk, IP risk, catastrophic event risk, litigation risk and technology obsolescence risk.

The other major type of valuation exercise involves looking at companies or transactions that are similar in size, sector, risks, market, business parameters etc. to the company under consideration (known as comparables or simply, comps), and look at their valuations/ prices in relation certain fundamental parameters such as sales, equity value, earnings, etc. (known as multiples) and attempt to determine the value of the firm under consideration by applying those multiples to the company’s own parameters. This method, although seemingly less rigorous than the discounted cash flow (DCF) method described above, is nevertheless the preferred method in corporate finance and with investors and bankers, because it required fewer assumptions, and is supposed to incorporate the value of the non-cash assets of the firm such as personnel, intellectual property (IP), brand name, etc. additionally, it incorporates factors such as economic cycles, market liquidity, sector optimism, etc. that are less well
captured and more difficult to incorporate using the more fundamental DCF method. The multiples/comparables method looks at the value of the firm from the viewpoint of either the entire firm, known as Enterprise value (Enterprise value = Equity value + Value of debt). However, as the decision-makers of the firm are the equity holders, there is also the consideration of equity value (enterprise value less payout to debt holders). It is important to make multiples comparisons consistent with the stakeholders, i.e. to have the ratios be consistent with the parameters used. Examples of ratios consistent with the value of the entire firm include Enterprise Value/ Sales, Enterprise Value/ EBIT (EBIT = earnings before interest and taxes), Enterprise Value/ FCFF (FCFF = free cash flow to firm). Examples of ratios consistent with value to equity holders include Price/ Equity (commonly referred to as PE ratio), Price/ Sales, Equity value/ FCFE (FCFE = free cash flow to equity). In our analysis, we have looked at the enterprise value multiples, because in most early stage medical device companies, there is not much debt and most of the financing is, as mentioned previously, a combination of equity and debt, held mostly by the investors/equity holders.

Another major consideration in valuing these companies stems from the immense value of real options that are embedded into their operations. Recognition of the values of these real options drives the staged investments that are often found in the financing terms of these companies, such that each stage of the company’s development is allotted some funds, with further funds committed only upon achievement of certain milestones. This allows the investors the option to have multiple decision points along the development milestones of the company, reducing risk and incorporating real option value. There is also a significant increase in the number of acquisition deals that incorporate Contingent Value Rights (CVRs) – rights to cash flows above and beyond the upfront payment from the acquirer contingent upon the acquirer’s reaching certain regulatory and sales milestones within a certain timeline following the acquisition. These CVRs often allow a deal to be culminated where
the acquirer and the target are in a logjam over agreement on the potential value of an uncertain major future event. Thus, CVRs (contingent value rights) provide a win-win situation for both the acquirer and the target, allowing the acquirer to withhold making an upfront payment on an uncertain future event, but providing the target the assurance of being rewarded contingent on the success of the same key events (typically regulatory or sales related milestones). It is obvious that the simplistic approach taken today in reporting these deals, which simply mentions the upfront payment and how much the potential payouts would total if all the CVRs were paid out, without applying the probabilities of success of the individual contingencies or even considering the time value of the relevant payouts grossly inflates the real values of the deals. Indeed, this is equivalent to saying that owning call options on a stock with a payoff of a million dollars a year from today contingent upon the stock price appreciating 100% over the one year is equivalent to owning the million dollars today. We understand that this is obviously not true, and that there are varying probabilities of success and time value of money. Can we come up with model to price the true value of these options? Yes, we can definitely come up with complicated option pricing models based off the binomial, Black-Scholes and other models, but the assumptions that we would need to build into these models would require to be individualized based on the terms of the CVRs (contingent value rights), and would again require assignment of some forms of probabilities/ volatilities to the individual events. Such models are being used by some quantitative shops, investment managers and banks, but are not in widespread use yet. For the purpose of this thesis, we decided to keep the analysis simple and used the simplistic enterprise values provided in the databases and the 10(k)s and other available public information sources and did not attempt to apply complicated models to value these CVRs.

Another factor for consideration is the fact that funds invested too have a temporal value, as does the convertible debt. It is entirely possible to use some sort of adjusted present value measure to the funds invested over time into the
company in the form of equity or debt and add to that or subtract from that the value of the embedded options as well as the value of payouts made over the lifetime of the company. A sophisticated investor considering making an investment into the company or an entrepreneur selling the company would look at all these factors.

Thus, we realize that there are many factors in the valuation process that impact the ultimate valuation that a medical device company receives. This is reflected in our models, and the manner in which they quickly turned more complex in the face of additional parameters. However, none of our models, starting from the simplest statistical measures, which obviously lacked standardization for many other variables, to the most complex multivariate models, which incorporated many of the variables, were unable to reach any level of significance. It may be that more complex models incorporating more parameters, and incorporating non-linearity into the data, or incorporating a complex option valuation parameter may ultimately provide us a statistically significant model. On the other hand, it is possible that the number of factors involved in the valuations, their inter-relationships, their relative weightings, acquirers' weightings of different parameters, and many other non-quantifiable parameters such as the purpose of the acquisition itself and the negotiations involve make coming up with a mathematical model to decipher the valuations a futile effort. Indeed, we are attempting to apply the techniques of quantitative trading to those of fundamental evaluation, which is a very difficult proposition. A fundamental valuation of each company based upon its merit may indeed be the best method for determining its value.
6. Conclusion:

The purpose of this thesis was to look at the impact of the CE marking approval on the exit opportunities and valuation of early stage medical device companies. This is especially important given the current regulatory environment in the US and the increasing challenges in accessing funding for these companies. We did a thorough retrospective review of mergers and acquisitions in the past ten years in the medical device industry, focusing specifically on strategic acquisitions of technologically novel early stage medical device companies. We consolidated data from multiple sources and extensively studied each company in the cohort. We used various direct or proxy measures to quantify both the events and the impact. We tested the outcomes rigorous statistical techniques to understand and quantify the impact of the event under consideration (CE marking approval) on the outcomes under consideration (time to exit and valuation). We also studied the impact of the events on certain normalized measures of the outcomes. Along the way, we developed models that could be useful in studying the impact of many other events on the outcomes studied in this thesis (time to exit and valuation) or on other outcome measures.

We found that the time to exit was significantly impacted by the achievement of the CE approval. Companies with CE approval only were faster to exit than those with no approvals, and those with both CE and FDA approvals were even faster to exit than those with only CE approval.

Regarding valuation, we did not find any statistically significant impact of achievement of the CE mark on the valuation (enterprise value) of the companies, nor on the return on investment (enterprise value/ funds invested), revenue multiple (enterprise value/ trailing revenue) or market fraction (enterprise value/ projected market) of any of these companies.
We conclude that from a time to market perspective, the CE marking approval alone is definitely beneficial for early stage medical device companies. Even more beneficial is achievement of both the CE and the FDA approvals or achievement of the FDA approval only, in that order of magnitude.

Regarding valuation, we conclude that valuation is an immensely complex exercise and that there were multiple moving parts that we have not taken into consideration in our analyses. Also, we made the presumption that the impact of any single variable on the valuation of the company would remain fixed over time, which is obviously not the case. Different acquirers have very different reasons for acquiring a firm, and these reasons change over time. Additionally, there may be many other factors in the valuation process that we have not considered in our model. Finally, historical data may not be the best representation of company valuation and valuations at different points in time may incorporate very different considerations.
7. Appendix:

7.A. Medical device regulation in the USA

Medical devices are defined by the US FDA as "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory that is:
- Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of it's primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes."

The FDA regulates a broad range of medical devices, including complicated, high-risk medical devices, like artificial hearts, and relatively simple, low-risk devices, like tongue depressors, as well as devices that fall somewhere in between, like sutures. FDA has authority to regulate medical devices before and after they reach the marketplace.

In general, devices are classified based upon their risk. Devices are classified into one of three categories—Class I, Class II, and Class III.

Class I devices are deemed to be low risk and are therefore subject to the least regulatory controls. For example, dental floss is classified as Class I device.
Class II devices are higher risk devices than Class I and require greater regulatory controls to provide reasonable assurance of the device’s safety and effectiveness. For example, condoms are classified as Class II devices.

Class III devices are generally the highest risk devices and are therefore subject to the highest level of regulatory control. Class III devices must typically be approved by FDA before they are marketed. For example, replacement heart valves are classified as Class III devices.

A manufacturer or company who wishes to sell its medical device in the USA has to demonstrate adequate levels of safety, efficacy and quality to the FDA. Depending on the classification of the device, the burden of this proof varies.

510(k) exempt medical devices: Medical devices that do not require FDA review before the devices are marketed are considered "510(k) exempt." These medical devices are mostly low-risk, Class I devices and some Class II devices that have been determined not to require a 510(k) (named for a section in the Food, Drug, and Cosmetic Act) to provide a reasonable assurance of safety and effectiveness.

These devices are exempt from complying with premarket notification requirements subject to the limitations on exemptions; however, they are not exempt from certain general controls. For example, 510(k) exempt devices must
- Be suitable for their intended use
- Be adequately packaged and properly labeled
- Have establishment registration and device listing forms on file with FDA
- Be manufactured under a quality system that complies with GMP (good manufacturing practices), and if applicable, GLP (good laboratory practices) and GCP (good clinical practices). These are broadly referred to as general controls.
Cleared medical devices: These medical devices are ones that FDA has determined to be substantially equivalent (SE) to another legally marketed device. A premarket notification, referred to as a 510(k), must be submitted to FDA for clearance. Most class 2 devices and some class 3 devices go through the 510(k) process before being placed on the US market. On average, 500-1000 510(k) applications are filed with the FDA’s CDER (Center for Device Evaluation and Research) annually. These represent approximately 95% of medical device approval applications filed every year.

Approved medical devices: Approved medical devices are those devices for which FDA has approved a premarket approval (PMA) application prior to marketing. This approval process is generally reserved for high-risk medical devices and involves a more rigorous premarket review than the 510(k) pathway.

The PMA process is the medical device equivalent of clinical trials for drugs. The PMA process involves filing for an IDE (Investigational device exemption) that allows the device to be used for the purpose of the trials. After sufficient bench and animal studies, an institutional review board (IRB) has to approve the trial. Then, a pilot or provisional trial has to be performed on a small number of patients to determine safety. This is the equivalent of phase 1 and phase 2 trials of the drug approval process. This is followed by the large scale, usually multi-center trial that is powered to demonstrate efficacy; this is known as a pivotal trial. These trials require appointment of a principal investigator (PI), who is usually a clinician, clinical investigators at each trial site, a trial manager and an external independent review Board. The results of the pivotal trial are then submitted to the FDA, who appoints an Advisory Committee, which is composed of a multi-disciplinary team including clinicians, nurses, engineers, regulators and others to determine the efficacy and safety of the device. The recommendation of the Advisory Committee is not legally binding, but is usually followed by the FDA in making its decision.
The PMA process usually is much longer and requires significantly higher investment on behalf of the sponsor (the company). Typically, there are approximately 40-50 PMA applications filed annually in the USA.

Recently, there are many reports of undue delays in approval by the US FDA. The importance of thorough screening and establishment of appropriate safety, efficacy and quality standards cannot be over-emphasized. However, excessive delay in the process, coupled with escalating costs may ultimately lead to stifling innovation and causing delay in access to latest technology and cutting-edge medical treatment. The FDA has recently launched initiatives to curtail this growing opinion, and has taken measures to improve the process. However, most medical devices still get approved earlier in the EU than in the US, and many new medical device technologies seem to be available in the EU long before they make their appearance in the USA.
7.B. Medical Device Regulation in the European Economic Region

There are three main directives governing medical devices in the EU.

1. Directive 90/385/EEC - commonly known as the Active Implantable Medical Devices Directive (AIMD Directive). This directive is concerned with powered implantable devices such as pacemakers.

2. Directive 93/42/EEC - commonly known as the Medical Devices Directive. This Directive covers the bulk of medical devices, from simple non-sterile drainage containers to complex devices such as interventional cardiology catheters.


These directives are transposed into the national rules of each member state, and apart from a few national differences, they provide the roadmap for medical device approval and compliance in the European Union.

All devices that fall within the scope of one of these directives must have the CE marking symbol to be placed on the European market. Most medical devices fall within the scope of the MDD (Medical Devices Directive). Only manufacturers who can demonstrate compliance with the MDD can affix the CE mark on their devices. It is important to understand that the CE mark is not a quality approval. It merely indicates that the manufacturer is in full compliance with the Medical Devices Directive or another directive.
CE marking is required in 31 countries in Europe. 27 of those countries are members of the European Union. Three additional European countries, Liechtenstein, Norway and Iceland, are not EU members, but are signatories to the European Economic Area (EEA) treaty. Finally, Switzerland is neither a member of the EU, nor a signatory to the EEA treaty, but it has transposed the Medical Devices Directive into national law and requires CE marking. These 31 countries, plus 3 other candidate EU countries, Croatia, Turkey and Macedonia, recognize the CE marking.

There are five main levels of authority and responsibility involved in the medical device regulatory process in Europe. These are:

1. The European Commission,
2. The Competent Authorities,
3. The Notified Bodies,
4. European Union Authorized Representatives, and
5. Manufacturers.

1. **The European Commission** consists of representatives from each European Union Member State and is headed by a President. It is responsible for the formal and practical implementation of the various treaties of the Union and the various rules pronounced by the Council of Ministers. It helps prepare the acts submitted to the European Parliament and the Council of Ministers. In addition, the commission acts to enforce the laws of the EU, acts to ensure the integrity of Europe’s integrated market, and administers the agricultural policies and regional development programs of the EU.

2. **The Competent Authority** is appointed by each EU member state and is responsible for medical devices. The competent authority will ensure effective implementation of the European Directives in that member state through transposition of the requirements into its national legislation. It also usually implements provisions for clinical evaluation approval as well as provisions for
processing post-production data from manufacturers. The competent authority selects and appoints suitable third-party, called notified bodies, to perform conformity assessments. The competent authority also acts as the clearing-house for consultation and exchange of pertinent information with equivalent authorities in other member states. It also takes actions such as instigating product recalls to safeguard public health from devices that pose or could pose unacceptable harm. Typically, the competent authority is the respective Secretary or Minister of State with responsibility for healthcare in the member state concerned.

3. **Notified Bodies** are the next level of responsibility for medical devices in the European union. Notified bodies are responsible for assessing a manufacturer’s continuing conformity to the requirements and for reviewing and approving Product Design Dossiers for Class 2 and Class 3 devices. European Product Design Dossiers are very similar in intention to US Pre Market Approval (PMA) applications. Notified bodies are generally designated by the Competent Authorities. With few exceptions, the notified bodies are entirely private sector or private sector affiliated organizations. Notified bodies are not involved in the conformity assessments of class 1 medical devices that are not sterile and do not otherwise have a measuring function, custom made devices, procedure packs or devices for clinical investigation.

The combination of European Commission, Competent Authority and Notified Bodies together is roughly equal to the role of the US Food and Drug Authority (FDA). The notified body is reasonably similar to FDA’s inspection branch. However, notified bodies do not have any legal or enforcement powers that exist within the inspection branch.

4. **An Authorized Representative** refers to an organization with an established place of business within the EU market, representing a manufacturer or other natural or legal person who does not have an established place of business in
the EU, but who intends to sell his medical device in the EU market. Typically, an authorized representative will be engaged in one or more of the following activities:

- Completing a company’s compliance route for establishing an impartial, independent European presence for all device classes
- Representing a company’s route for registering Class I (non-sterile/ non-measuring) devices manufactured within the EU (if the company is based outside the EU).
- Serving as a company’s representative for complaints and other notifications to the appropriate Competent Authority for all device classes
- Responding to compliance enforcement communication and instruction by the Competent Authorities.

It is important to note that companies that do not have an established place of business in the EU must appoint an EU Authorized Representative to act as the company office communication link with the in the EU.

5. Manufacturer or the person placing the product on the market is the last link in the communication and authority link. To enter the EU market, the manufacturer must make sure that his product complies with all the requirements of the EU. The manufacturer is responsible for:

- Clearly defining the intended purpose of the device to be CE marked
- Obtaining the appropriate assessment certificates as per the selected Conformity Assessment Procedure
- Selecting the relevant technical standards to be used to demonstrate conformity
- Creating, updating and retaining technical documentation at the disposal of the Competent Authorities
- Implementing and operating a post-market vigilance system to inform the Competent Authorities of reportable incidents
- Ensuring that the device conforms to the relevant Essential Requirements
- Making a written declaration that the device conforms to the requirements of the Directive

Once all the above requirements have been met, the manufacturer may affix the CE mark of conformity to the device.

The CE mark of conformity is the symbol that must be affixed to every product placed on the European market according to the relevant Directive issued by the European Commission. The CE mark is meant to indicate conformity of a given product with requirements for various properties. The properties are usually technology sector specific, although certain commonalities abound between directives. For medical devices, the CE mark indicates not only conformity with the Medical Device Directive but also to the requirements of any other Directive relevant to the product that provide for CE marking. The manufacturer is required to specify which directives the product complies with in the technical documentation with the product. For companies without a European office, inclusion of a name and contact number information of the EU Authorized Representative is part of the requirements of the EU marking.

Medical devices in the EU are grouped by classification. They include:

1. Class I devices – These include devices that are not sterile and do not have a measuring function. These are low risk devices like examination gloves. A second category of class 1 products are devices that are provided sterile such as sterile bandages, or have a measuring function, such as patient measuring scales.
2. Class II devices – These are medium risk devices and are further sub-classified into 2 groups:

   Class IIA devices - these include a wide range of devices such as diagnostic equipment, hearing aids and electrocardiographic devices.

   Class IIB devices – these include devices that pose a greater risk, such as surgical lasers, ventilators and other devices whose failure can cause a severe health risk to the patient or the user.

3. Class III devices – This is the highest risk category. Cardiac catheterization devices and heart valves fall into this category and they often require lengthy clinical trials prior to their approval.

There is a set of rules in Annex IX, which are utilized to determine the device classification. Proper classification of the device is essential since it determines the path to regulatory compliance with the directive.

Medical device manufacturers, except those that manufacture the most basic devices must implement a Quality Management System (QMS) in compliance with the Annex II or V of the Medical Devices Directive (MDD). To meet those requirements, most companies apply the ISO 13485:2003 standard, which is a quality management standard designed specifically for medical device manufacturers. ISO 13485 is not mandatory and there are other ways medical device manufacturers can comply with Annex II or V. However, most companies apply ISO 13485 quality standard simply because this certification presumes compliance with Annex II or Annex V for Quality Management Systems. Class I devices that are not sterile and do not have measuring function do not need a full Quality Management System that is inspected by a Notified Body.

While the Quality System is being implemented, which can typically take between 3 to 9 months, depending on the size of the company and the activities performed, a Technical File has to be prepared. This is a compilation of technical
documentation relating to the efficacy and safety of the device and its components include:

- Device description
- Intended use
- Product specifications
- Technical Drawings
- Instructions for use
- Packaging and labeling
- Clinical data
- Risk analysis
- Performance testing
- Manufacturing documentation
- Standards used
- Other important technical data

A technical file is required of all devices including low-risk class I devices. Technical files for high-risk class III devices are called as Design Dossiers and are more complex and require extensive clinical data. The Technical Files, except for class I devices that are non-sterile and do not have measuring function, are audited along with the Quality System by a Notified Body. The Notified bodies are independent auditing companies that have been authorized by EU member states' Ministry of Health to conduct annual audits of medical device companies and their products in accordance with the Medical Devices Directive.

Once the Technical file has been competed and the ISO 13485 quality system has been implemented and is operational, the company needs to appoint an Authorized EU Representative, if the company has no place of business in the EU. The Authorized Representative, also called as the EC Rep, acts as the regulatory liaison between the medical device company and the European countries' Ministries of Health, also known as the Competent Authorities.
Regardless of the class of the device, the medical device company is required to have an Authorized Representative. The Authorized Representative has to be located in Europe and must be qualified to handle regulatory responsibilities that may be delegated by the manufacturer. The Medical Devices Directive requires that the Authorized Representative have access to the Technical Files if the competent authority requests a review of the same. The authorized representative may also be required to perform certain tasks on behalf of the manufacturer, including registration of the device, incident reporting, assisting with product recalls, change notifications to competent authorities, etc. The Authorized Representative’s name must appear on the device labeling throughout Europe.

Manufacturers of class I non-sterile, non-measuring devices do not need to implement a full quality system, and their technical files are not audited by a notified body. Instead, they are required to self-declare their conformity with the Medical Devices Directive. For all other device classes, once an Authorized Representative has been appointed, the Quality management system and technical file must be audited by a notified body that is selected by the manufacturer.

Once the Technical File review and Quality system has been successfully audited by the Notified Body, the device manufacturer is issued a Notified Body CE marking certificate. Maintenance of the certification requires annual audit by the Notified Body. Class I devices that are not sterile and do not have measuring function are not issued a CE marking certificate since conformity with the directive is based on self-certification. All class I devices need to be registered with the Competent Authority where the company’s Authorized Representative is located. Most EU countries do not require registration of class I, class IIA and class IIB devices because they are subject to annual audits by a notified body. One exception to this rule is Italy, which currently requires all devices to be registered regardless of their classification.
Once all the CE marking compliance steps have been fulfilled, a Declaration of Conformity will need to be prepared. The Declaration of Conformity is typically a one-page, legally binding document on company letterhead stating that the company is in full compliance with the Directive. It includes:

- Identification of the device
- The name of the EC Rep
- Device classification
- Route to compliance
- Name of Notified Body
- CE marking certificate number

Finally, it must be signed by an authorized representative of the company. An electronic signature is acceptable.

Although not explicitly addressed in the MDD, national laws often require translation of the labeling and instructions for use into the national language of the country into which the device will be sold, unless an exemption has been granted by a competent authority. Translation of documentation is an important step in maintaining compliance with the national requirements.

After achieving the CE marking certificate, the product still has to be registered with the competent authority in some EU member states. There are specific pre and post market medical device registration requirements in certain states above and beyond the CE marking.

Finally, after placing products on the European market, the company has to continue to monitor its safety and efficacy. This means incident reports have to be appropriately handled in accordance with European requirements and have an effective post market surveillance process in place. It is also necessary to
systematically review experience gained from having the device in the field and implement corrective action as required.
7.C. Medical device regulation in Canada:

In Canada, medical device companies need to demonstrate compliance with the Canadian Medical Device Regulations (CMDR).

Medical devices are classified into 4 classes in increasing order of riskiness. Class 1 devices need a Medical Device Establishment License (MDEL) to be approved by Health Canada. Class 2, 3 and 4 devices require a Medical Device License (MDL). When compared to the US FDA 510(k) registration process, the process of securing a Canadian MDL is usually faster for Class I devices, about the same for Class III devices and more complicated for Class IV devices.

Class II, III and IV device manufacturers require implementation of ISO 13485:2003 quality system to meet Canadian requirements. The quality system must be audited each year by a Health Canada certified Registrar. Most large European Notified Bodies are also authorized to conduct audits in Canada as Registrars.

Class 3 and class 4 devices also require submission of Premarket Review Document and may require inclusion of clinical trial data. Data from trials conducted in the US or Europe may be acceptable.
7.D. Medical device regulation in Japan:

Japan's Pharmaceutical and Medical Devices Agency (PMDA) is the regulatory agency and works with the Ministry of Health, Labor and Welfare (MHLW) to regulate medical devices in Japan in accordance with the Pharmaceutical Affairs Law (PAL) and Ordinance #169. Japan's medical device classification system differs from that of the US and Europe and determining classification is based on Japanese Medical Device Nomenclature (JMDN) codes.

The process then requires appointment of a Marketing Authorization Holder (MAH) or a Designated Medical Authorization Holder (D-MAH). The D-MAH acts on behalf of the foreign manufacturer to register the medical device under the Foreign Special Approval System. The next steps involve submitting application for a "Foreign Medical Manufacturer Accreditation" (all device classes) and a PMDA (Pharmaceutical and Medical Devices Agency inspection (for class 2 – controlled medical devices and upward). The manufacturer must also implement ISO 13485 Quality Management System (QMS) that also complies with PAL (Pharmaceuticals Affairs Law) and MHWL (Ministry of Health Labor and Welfare) Ordinance #169. Further steps involve preparation of STED (Summary Technical Document) and a pre-market approval (PMA – for class 2 –controlled medical devices and upward). A QMS (Quality Management System) audit is then performed by a Registered Certification Body (RCB), which are independent companies authorized by the Ministry of Health, Labor and Welfare to certify Specified Controlled Medical Devices and issue Pre-Market Certifications, in case of class 2 – specified controlled medical devices. For higher classes of medical devices, the QMS audit is performed by the PMDA (Pharmaceuticals and Medical Devices Authority) or by a prefectural regulatory authority.
7.E. Medical device regulation in China:

The State Food and Drug Administration (SFDA) regulates medical devices in China. Once the device has been appropriately classified in accordance with SFDA Order #15, a Legal Agent and After Sales Agent located in China would have to be appointed, who would then coordinate and control the SFDA device registrations.

Clinical trials may need to be conducted in China for Class 2/3 devices that do not already have regulatory approval elsewhere in the world, long-term implantable devices or certain other high-risk devices. If clinical trials have been conducted outside China and the device has US, European or other national approval, the data will likely be accepted by the SFDA.

Foreign manufacturers are also required to submit notarized proof of compliance with a Quality Management System (QMS), such as ISO 13485, US FDA GMP (Good Manufacturing Practices) or other national quality system regulations. Finally, a Chinese Registration Standard Document and an Import Medical Device Registration Certificate (IMDRC) needs to be prepared and submitted to the SFDA for approval, along with the device. The SFDA Medical Device Quality Supervision and Inspection Center conducts testing on the device and issues the IMDRC, which is typically valid for a period of five years.
7.F. Medical Device Regulation in India:

Medical device regulation in India has been implemented since 2005. Medical devices in India are regulated by the Central Drugs Standard Control Organization's (CDSCO) Medical Devices Division. This organization is overseen by the Drug Controller General of India (DCG(I)), who is appointed by the Ministry of Health and Family Welfare.

The major steps involve determining whether the product fits the list of regulated medical device categories, preparation of product registration application (including Forms 40 and 44), payment of registration fees, appointment of an Indian Agent as the company’s official representative, submission of Plant Master File and Device Master File, and coordination with the DCG(I)/ CDSCO to address follow up issues.
The value creation paradigm is unique for medical device companies. At each step of the chain, value is created, and every milestone reached converts to a higher probability of ultimate success. Also, success for companies in the medical device space typically tends to be more likely than that in the pharmaceuticals or biologicals space. The times to exit are also shorter and the investments typically lower than that for pharmaceutical development. These factors make the barriers to entry lower and the improve possibility of carrying the product further along the development and marketing pipeline. This, combined with the opportunity to significantly impact the management of a disease and make significant contribution to lowering the suffering from a disorder makes the field very attractive and rife for bright entrepreneurs with early stage companies and innovative technologies.

The first step involves identification of a need and development of a technology/solution that can address the need. Then, after deliberations with clinicians, patients, other stakeholders and existing literature, one realizes the novelty of the idea and its application. This is the ideal time for protecting the intellectual property and filing for a provisional patent. Further development of the idea, coming up with a prototype, development of a laboratory model of the disease and prototype testing are the next steps. Upon conviction of a real tangible novel solution, a final patent filing is in order. The ideal patent is broad enough to cover the entire space and prevent others from infringing it through cosmetic modifications, and narrow enough to not be invalidated. It may also be important to look at existing patents in the space and understand one's free

The process then involves developing the prototype further, bringing together a team, involving key clinicians, writing up a systemic business plan and approaching investors to raise funding for further development. Somewhere along these stages, the company may be incorporated, with the appropriate
assignee status for the patent. Further development involves laboratory testing on appropriate animal models. Once animal data on appropriate disease models is completed and the results are promising, a major value inflection point is reached. This may be another appropriate point to raise funding, as the further needs are likely to be much greater than was the case up until this stage.

The next steps involve determination of the class of the device. Class I devices are deemed to be low risk and are therefore subject to the least regulatory controls. Class II devices are higher risk devices than Class I and require greater regulatory controls to provide reasonable assurance of the device’s safety and effectiveness. Class III devices are generally the highest risk devices and are therefore subject to the highest level of regulatory control. Class III devices must typically be approved by FDA before they are marketed. Usually, a new technology will be a class II or class III device. The next steps in the process include involvement of the regulatory bodies, discussion with them about our proposed plan of development (pre-IDE meeting) and soliciting feedback. The next steps may involve, as necessary, filing of the IDE, appointment of appropriate clinical investigators and team, running of the appropriate preliminary and pivotal trials and gathering data on the safety and efficacy of the device. Many early stage device companies may outsource part or whole of these steps to a clinical research organization (CRO). This process may take anywhere from 1 to 5 years or more, depending on the device and the type of claims.

Finally, the data is submitted to the FDA, who appoints a review committee, consisting of scientists, clinicians, academicians, policy makers, engineers and others, to make recommendations. The decision of the review committee, while not legally binding, is usually upheld by the FDA. Approval of the device by the FDA is another major value inflection point for the company. The route for CE approval, while not exactly the same, does follow a similar process as that of the FDA approval and was described in detail earlier in the discussion.
Unlike pharmaceuticals, FDA approval is not the step that creates the majority of the value in medical devices. The steps after that, including adoption by physicians, achievement of reimbursement, incorporation of the device and the procedure into existing CPT codes or creation of a special code for the device, widespread use of the device and ultimately, achievement of status of “standard of care” are important value creation points for this device, and a large portion of the future of the device depends on these post approval steps.

In our research, we have attempted to include each of these value inflection points by using either the point itself or some proxy for the same to represent achievement of the same by the companies that we studied. The following list provides the major value inflection points for medical devices development and our proxies for the same:

<table>
<thead>
<tr>
<th>Value inflection points</th>
<th>Measure/ Proxy measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Development of the idea</td>
<td>Patents/ date of patent issue</td>
</tr>
<tr>
<td>2. Incorporation of the company</td>
<td>Date of incorporation</td>
</tr>
<tr>
<td>3. Completion of lab/ animal studies</td>
<td>IDE filing status</td>
</tr>
<tr>
<td>4. Approval status</td>
<td>CE (Y/N), date of CE filing, FDA (Y/N), date of FDA filing, type of filing (PMA/ 510(k))</td>
</tr>
<tr>
<td>5. Reimbursement</td>
<td>Previous years' revenue</td>
</tr>
<tr>
<td>6. Adoption status</td>
<td>Potential market/ revenue</td>
</tr>
<tr>
<td>7. Value created prior to acquisition</td>
<td>Funds raised</td>
</tr>
<tr>
<td>8. Value created at the time of the acquisition</td>
<td>Enterprise value (exhaustive EV, not just the price paid)</td>
</tr>
<tr>
<td>9. Acquirer related information</td>
<td>Synergy value for acquirer, Potential market, LTM stock returns, Market cap of acquirer</td>
</tr>
</tbody>
</table>

We shall now look at the exit opportunities for these medical device companies.
7.H. Exit opportunities for Medical Device companies:\(^4\):

Not all medical device companies seek to exit. It is important to understand why medical device companies would seek to exit. We address this from the business viewpoint and from the financial viewpoint.

The medical device industry is a highly consolidated space. It is of the form of an oligopoly – a few big players dominate the majority of the market. This gives them huge economies of scale and scope, especially in the manufacturing, development, sales and marketing, distribution, post sales support, political lobbying and risk and liability management arenas. Also, it provides portfolio diversification in a highly risky regulated business that is riddled with uncertainties. Thus, there are many advantages to being a large consolidated player in the space, and it is not surprising that market economics has resulted in the appearance of a natural oligopoly.

From the perspective of the new entrant in this space, there exists a huge competitive landscape from rivalry among existing players, who are involved in intense competitive strategies to maintain and enhance their positioning. The new entrant in the space does not have much leverage with downstream distributors and customers, other than the excellence of the device/ technology itself. Upstream, the only source of power they hold is the patent rights. Raw material suppliers, especially if the technology requires some specific raw materials that are not easily available on the open market may also be the source of channel pressure. Manufacturing is usually outsourced and may be done in-house, but is expensive to set up, run and maintain. Threat of new entrants with better technology is always present as is threat of substitutes. Additional concerns around stringent regulatory pressures and consume health risk and liability issues all add to the competitive pressures in the medical device space for a new entrant early stage medical device company.
The one major advantage of an early stage medical device company in this challenging industry, one that constantly attracts new entrants and fuels the system, is the need for research and innovation. The behemoths have long since realized that they are not the best sources for encouraging research and innovation. Hence, most large medical device companies, in addition to in-house research teams, have large business development teams who seek smaller innovative companies with novel products to add to their own innovation pipeline. This presents the largest and most strategic opportunity for early stage medical device companies for an exit. The advanced stages of development (arguably) and the manufacturing, distribution, marketing and sales (definitely) are the forte of the behemoths.. the large consolidated medical device companies. Also, the skills and capabilities required in the advanced stages of the development, sales and marketing are significantly different from those required at the early innovation stage. Hence, it makes strategic sense for an innovator, entrepreneur or medical device developer to do what they do best (innovate and early stage development) and then hand over the company/ product (at the right price) to a strategic acquirer for further appropriate development and outreach.

This is not to argue that all medical device companies should go the exit route, or even that strategic acquisition is the only route to exit. There are medical device companies that are well established in their niche, and do not feel the need for an exit. Others go on to perish for lack of either a pressing need for the product, a minor glitch in the development process or lack of funding, among other causes. There are others that exit or continue on through an IPO (Initial Public Offering) and may even go on to be a large device company with multiple products and a diversified portfolio, capable of competing in its own right as part of the oligopoly. However, these tend to be the exception rather than the rule.

Since strategic acquisition is the exit route for the vast majority of successful early stage medical device companies, we have used it as the benchmark for looking at the exit opportunities and valuation impact of the CE marking approval,
which is but one of many important value inflection points in the entire life cycle of the company.
7.1. Funding early stage medical device companies\textsuperscript{14,15}:

The main sources of funding for early stage medical device companies are personal funds, friends and family, angels, grants, strategic partnerships and venture investors. At later stages, the company may be able to attract more advanced capital such as from licensing of patents, private equity and some other innovative methods of financing such as contingent value rights (discussed in detail in the section on valuation). It is only in the more advanced stages of development that a company can get access to bank financing or capital markets for debt or equity financing.

For the early stage medical device entrepreneur, funding is a major challenge, and a constant balancing act. Multiple strategic decisions are made along the way, and ensuring ongoing funding for the company is paramount to avoid the proverbial "costs of financial distress", which in these cases can actually lead to the demise of a potentially breakthrough product.

In the face of such challenges, the entrepreneur is called upon to make decisions on the appropriate distribution of scarce capital. Concerns regarding the prolonged time lines and corresponding increasing costs in the face of increasingly challenging funding environment are driving many early stage medical companies to make the strategic decision to upfront go for CE approval, market in the EU, become cash flow positive and then return to the USA for seeking approval and marketing. This results in actually pushing off innovative technologies overseas, delaying or at times depriving the US access to the latest and best medical technologies due to issues arising from funding the FDA approval process.

From the perspective of value creation, getting cash flow positive and self-sustaining definitely triggers off a major value infliction point in the life cycle of the company. It not only provides infallible proof of concept and marketing capability,
but also significantly improves the negotiating position of the company. The question then is: is this a good strategy? Should more companies pursue the same? Should investors push their portfolio companies to follow this strategy? Should directors on the board of these companies advice their management to follow such action? What are the advantages and disadvantages of doing so?

We have attempted to answer some of these questions and to present an insight into the pooled data over the past 10 years of similar companies as that who would face such questions. We have used the time to exit (TTE), post-approval fraction (TTE/ time since incorporation to exit) to study the temporal effects of the CE mark acquisition and the Enterprise value (EV) and some EV normalizing ration (EV/ Funds Invested – a measure of return on investment, EV/ Revenue and EV/ Projected markets) to study the valuation impacts of such a strategy.
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