CRITICAL FACTOR IDENTIFICATION IN MEDICAL DEVICE DEVELOPMENT THROUGH SUPERVISED LEARNING

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ABSTRACT

This paper investigates the impact of different variables in Medical Device Development (MDD), where FDA (Food and Drug Administration) approval time is considered as a performance variable. To analyze the significance of the variables supervised Bayesian learning, the Minimal Description Length (MDL) algorithm, is used. A set of real FDA data, representing 474 different companies in USA medical device markets, from 2400 FDA approved orthopedic devices is used. The aim of the study is to identify which product, company and regulation factors contribute most to the variations in FDA decision time.

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1   INTRODUCTION

Although advances in technology provided many invaluable medical products to improve human health and sustain it, the development cost of medical devices burdens the healthcare systems as the industry is more technology-centric than ever before. As such, the identification of critical success factors for medical device development (MDD) has become increasingly important. Many factors are related to the likelihood of success for devices in the market; and according to the company's ability to make changes, these factors are considered to be either internal or external (Medina et al., 2012). Internal factors include the organization's composition in terms of the level of experience of the design teams (Lucke et al., 2008), along with an effective communication of the development priorities (Brown et al., 2008). Likewise, the execution of a complete development process (i.e., preliminary market analyses, financial analyses, and customer involvement) is important (Brown et al., 2008; Rochford and Rudelius, 1997; Millson and Wilemon, 1998). On the other hand, external factors are mostly related to costs and profits from the customers' vantage point, research and development (R&D), clinical research and insurance companies' reimbursement (Advanced Medical Technology Association, 2003). Specific issues are also addressed pertaining to intellectual property protections and overseas market opportunities. More importantly, the Food and Drug Administration (FDA), regulatory agency of medical devices marketed in the Unites States, has been identified as the primary factor influencing the development priorities (Advanced Medical Technology Association, 2003).

Existing methods used for the identification of critical success factors have a number of shortcomings, such as the subjectivity of survey-based studies and the ability to comprehensively and rigorously address both internal and external factors (Medina et al., 2012). This paper addresses these shortcomings with the application of a Bayesian network (BN) approach to examine the impacts of product, company and regulation related factors on MDD performance. BN is a well-known data mining method, widely applied in medical diagnosis (e.g., Nikovski, 2000; Wu et al., 2007). Furthermore, it has been cited in the literature as a preferred method to address the limitations of other analyses methodologies (e.g., Venter and Van Waveren, 2007; Kim and Park, 2008). This approach allows for a scientifically objective analysis with the ability to simultaneously consider quantitative and qualitative data (Chiang and Che, 2010; Venter and Van Waveren, 2007).

In the paper, we use the BN approach to investigate the critical factors of MDD. BN analysis is performed using data from 2400 FDA approved orthopedic devices. In the remaining sections of the paper, we first provide a summary of the reviewed literature in relation to the application of BN with implications on MDD; then, we introduce the methodology. Details about the data set and results follow before we provide conclusions.

2   LITERATURE REVIEW

BNs have been successfully implemented in MDD to mitigate risks and failures, improve new product development and provide medical diagnosis. Jiang et al. (2011) focused on the assessment of medical device risks and failures in the field to proactively solve issues in the manufacturing process or the supply chain. Their methodology involved a Health Hazard Analysis (HHA) that was based on BNs. Meanwhile, Rieger and Rahimi (2011) developed a Bayesian risk identification model (BRIM) as a mitigation strategy for human response failures related to the combined effect of interface, environment, and contextual influences (Rieger and Rahimi, 2011). For decision making, Atoui et al. (2006) used a BN approach for the risk prediction of cardiovascular events based on the patient's data stored in a personal Electrocardiography (ECG) monitor and demographic information. They concluded that the BN approach provided better results in comparison with neural networks and logistic regression models. Velikova et al. (2011) presented a similar application of BNs, in order to predict the evolution of preeclampsia in pregnant women.

New product development has been improved with BN approaches that allow for iterative economic evaluations of new devices as part of the cost-effective analysis of the development process (Vallejo-Torres et al., 2008). Iterative economic evaluation started from early stages of the development process and continued with the addition of evidence throughout the development process. Yang (1997) focused on the last stage of the development process with a BN approach for the forecast of sales for new devices based on historical data on earlier launches and expert feedback.

BNs have been widely applied for medical diagnostics. For example, Patrocinio et al. (2004) used BN to classify clusters of micro-calcifications for mammography diagnosis of breast diseases. While BNs

are mostly used for small to moderately large devices, it has also been demonstrated that BNs are advantageous for the diagnosis of medical problems with large complex devices (Veronique et al., 2007). In support of these applications, Nikovski (2000) defined engineering techniques to manage data issues such as incomplete or partially correct numerical probabilistic information.

Due to benefits of the BN approach, it has been selected as the methodology for this work in an effort to overcome the limitations of the prior research in this field. The studies investigating critical factors for MDD have been mostly limited to survey-based studies (Brown et al., 2008; Rochford and Rudelius, 1997; Millson and Wilemon, 1998; Advanced Medical Technology Association, 2003) or only featured data analysis implementing statistical techniques (e.g., ANCOVA by Medina et al., 2012). Survey-based studies are subject of criticism for their subjectivity along with the lack of comprehensiveness and thus non-generalizable results. Consequently, prior research included the analysis of FDA approved orthopedic devices and the impact of multiple factors in FDA's decision time (Medina et al., 2012). Even so, the strong correlations between many of the variables did not permit a comprehensive evaluation. As a result, BN approach is implemented here, and is considered to be a more robust technique for this analysis.

3   RESEARCH OBJECTIVES AND METHODOLOGY

Medical device development processes are largely unexplored in detail. However, MDD is considered to be a particular development process due to high safety needs and the potential impact on human life. Increasing complexity of medical devices is also adding challenges to the development process. Therefore, the aim of this research is to identify critical factors to improve the efficiency of the MDD process. In this domain, access to historical data is very difficult; the only data source at this point is FDA. Furthermore, as these factors are relevant to all companies in this sector, we believe that investigating the critical MDD factors would be of great interest for these companies.

In an effort to identify critical factors of MDD while responding to weaknesses in the summarized earlier research, we have opted for a BN based approach, and devised the research methodology shown in Figure 1. The choice of using BN based data mining and exploration is motivated by the advantages that BNs present when exploring different data and uncertainty modeling capabilities.
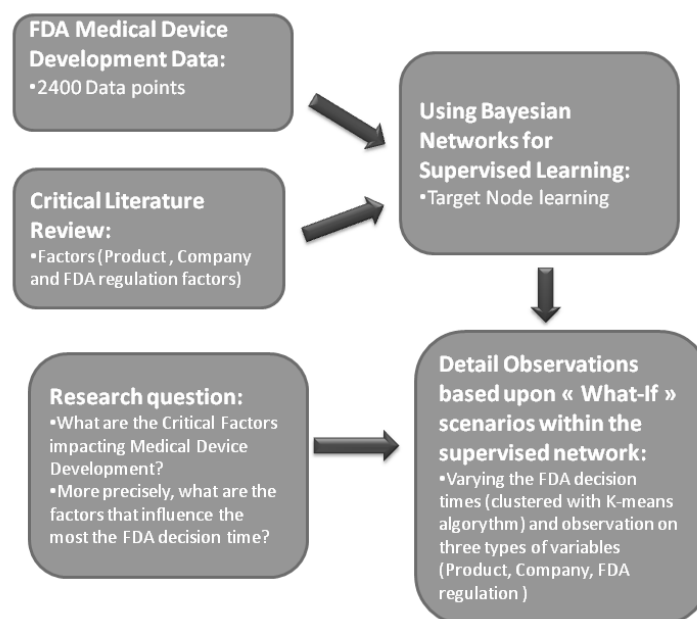
Figure 1. Research Methodology

We chose to use actual data. Examination of various factors also required combing through the published sources in engineering and business literature focusing on product development. This process helped us compile the potential factors. We have then carefully chosen the algorithms for the BN application; and finally, conducted what-if scenarios to ensure a comprehensive analysis. Further details about these are provided below.

4   DATA AND VARIABLES

Data availability was dependent on the number of FDA approved orthopedic devices to date. As a consequence, the raw data did not have an equal number of samples per category, i.e., product codes[1]. From the complete data set of 9013 orthopedic devices (from 166 product codes), some product codes only had one data point while others had hundreds of data points. Only a subset (24) of these product codes was found to consistently have more than 100 data points for each code. In order to account for equal representation and hence omitting undue bias, we have randomly selected 100 devices per product code and included them along with their full FDA dataset. As a result, 2400 FDA approved orthopedic devices were randomly selected to study the critical factors of MDD.

The variables associated with the regulatory environment include different types of classifications, such as submission type, regulation number, but also evaluate the level of experience of FDA with historical reference (HR) per body part, function and material. The HR is used to measure the level of experience in multiple aspects by quantifying the number of devices previously approved with the particular characteristic. The company experience is also considered, with the company's HR measuring the number of devices previously cleared/approved for the same company. Other variables associated with the company include the name of the applicant company and the year of submission. Finally, variables associated with the product are several, ranging from different types of classifications (e.g., product code and risk classification) to product specific characteristics. Some of the product specific characteristics include the material, intended use, context of use and body part, among others. The performance measure (dependent variable) in the analyses is the FDA decision time. This value results from the calculation of the elapsed time between the company's submission date and FDA's decision date.

5   ASSOCIATION DISCOVERING AND LEARNING ALGORITHMS WITH BAYESIAN NETWORKS

In general, a BN network represents a graphical visualization of a set of "fuzzy" cause-effect rules that support different types of reasoning and predictive modeling. BNs are represented using directed acyclic graphs (DAGs) (Jensen and Nielsen, 2007), where the network is defined through a couple, *BN=(S, P)*. *S=(N, A)* represents the structure (i.e., the graph) and "*N*" is a set of nodes. Each variable is represented as a set of mutually exclusive states. "*A*" is a set of edges representing the causal interaction between variables. The link from node N1 to N2 is defined as "*N1 is a parent of N2*", and represents the fact that if we know the information on N1 then we can deduce the knowledge on N2.

P represents a set of *conditional probability distributions* that define the probabilistic dependency between a node and its parents. Conditional Probability tables associated with each state of the variables are calculated, and provided for all variables using a generalization of the well-known Bayes Theorem (shown below):

$$ P\left(\frac{A}{B}\right) = \frac{P\left(\frac{B}{A}\right) * P(A)}{P(B)} \qquad (1) $$

In this study, we used a large data set (N=2400) and based our observations on supervised learning in order to explore the relationships between the whole data set. The algorithms used in this work are developed by Jouffe and Munteanu (Jouffe and Munteanu, 2000; Jouffe and Munteanu, 2001; Munteanu and Bendou, 2001), and are based on the widely known Minimum Description Length Principle (MDL) proposed by Rissansen (1978).

6   RESULTS & DISCUSSION

We have used BayesiaLab 5.0 to build the relations network and then to calculate the joint conditional probabilities. As described earlier, we have used 2400 FDA approved orthopedic devices with the variables discussed. In the overall analysis 20 variables have been used (see Annex 1). However, supervised learning has pointed out 10 variables of direct impact on the Time of decisions (Figure 2). In the figure, as defined per our literature review and established categorization of variables (presented in Medina et al., 2011; Medina et al., 2012a; Medina et al., 2012b), red nodes indicate product

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[1] Product codes are FDA classifications used to group medical devices with the same characteristics and requirements.

associated variables, yellow nodes indicate company related variables, and green nodes show the regulatory environment related nodes.
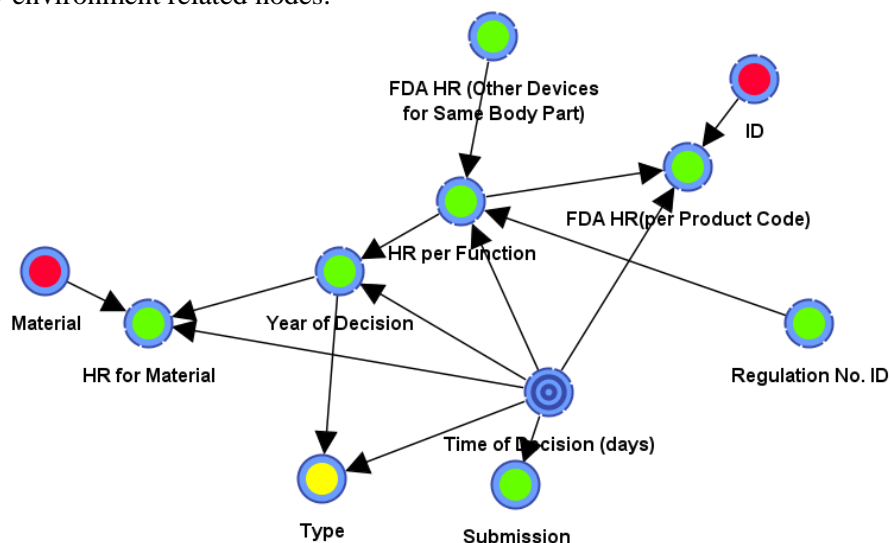

Figure 2. Supervised Learning Using the Sons and Spouses Algorithm

The structure of the network suggests that FDA decision time is related to FDA HR (per product code), Submission year, Year of Decision, HR per product function (representing company know-how in this process), HR for Material, and Type of Submission. This means that the information on these variables supports the inference on Time of Decision. Indirectly, we can see that the Regulation No. ID is related to the HR per Function showing that for some types of devices the delay is impacted by the information on security and patient safety such as materials used and risks associated, and also related to the FDA HR (Other Devices for the Same Body Part) showing that some types of devices have been investigated longer by the FDA. HR per Function is related to the Year of Decision, and this relation shows trends in medical device development and approval. This fact is underlying the necessity of a company to investigate FDA priorities in term of health security. Year of Decision has probabilistic inference with the Type of Submission and HR for Material.

7   INVESTIGATING THE IMPACT ON FDA DECISION TIME

Upon review of the network structure, the detailed observations are provided for "What-If" scenarios. This approach aims at varying the FDA Decision time, as a targeted variable, to make detailed observations of the change in distributions of observed variables. The FDA decision time distribution was divided into meaningful groups using K-means clustering.

We can observe that the FDA decision time is less than 139 days (Figure 3) in 73.88% of cases. Initial (observed on the given dataset) distributions show that the majority of submissions are 510k and that in most of cases it concerns Special type (23.66%) or Traditional type (74.59%). Furthermore, in majority of cases we can observe that Company HR (67.25%) is less than 72.5. This decision relates mostly to Bone, Hip and Spinal body parts. The context of use is surgery operations; and the functions of the product are fixation (in 58.33%) and Prosthesis (29.17%). It can also be seen that in 95.83% of cases, risks classification is 2.

If the FDA decision time is less than 139 days, we can see that it concerns 30.66% of the Special type and 68.28% of the traditional type. Five percent more of special types are concerned with this type of decision. There are also slight variations in distribution of HR for material and HR per Function.

When the FDA decision time is between 139 and 354 (1 year) (Figure 5), we can observe changes in type of submissions. The traditional type is represented in 92.56% cases and Special cases represent only 4.84%. We also observe the changes in the year of decision; it appears that the FDA decision time is higher between 1997 and 2001. This can be explained partially with the FDA policy change, supporting the effort to diminish the decision time and time to market for the companies.

As for the FDA decision time greater than one year (Figure 6), we can observe that 92% are of the Traditional type and 6.51% are Original types. Original types induce always greater decision time, and in this case larger than one year. This is expected; in order to ensure the security of patients, FDA takes more precaution and time to investigate potential impact and safety issues of the strictest pathway given that the Original type is only for the Pre-market approvals (PMA). It can also be seen that this decision time was more prevalent between 1997 and 2001. Around 30% of cases have been investigated in this period. There is also a decrease in this long decision time after 2004. Eight percent less of cases are observed to be waiting for a FDA decision that is longer than a year. 11% more in cases of HR for Material are between 831 and 1410. The changes can be also observed in the distribution of HR per Function. An increase of 12% of HR per Function are observed for less than 943, and 8% decrease in larger than 3193.
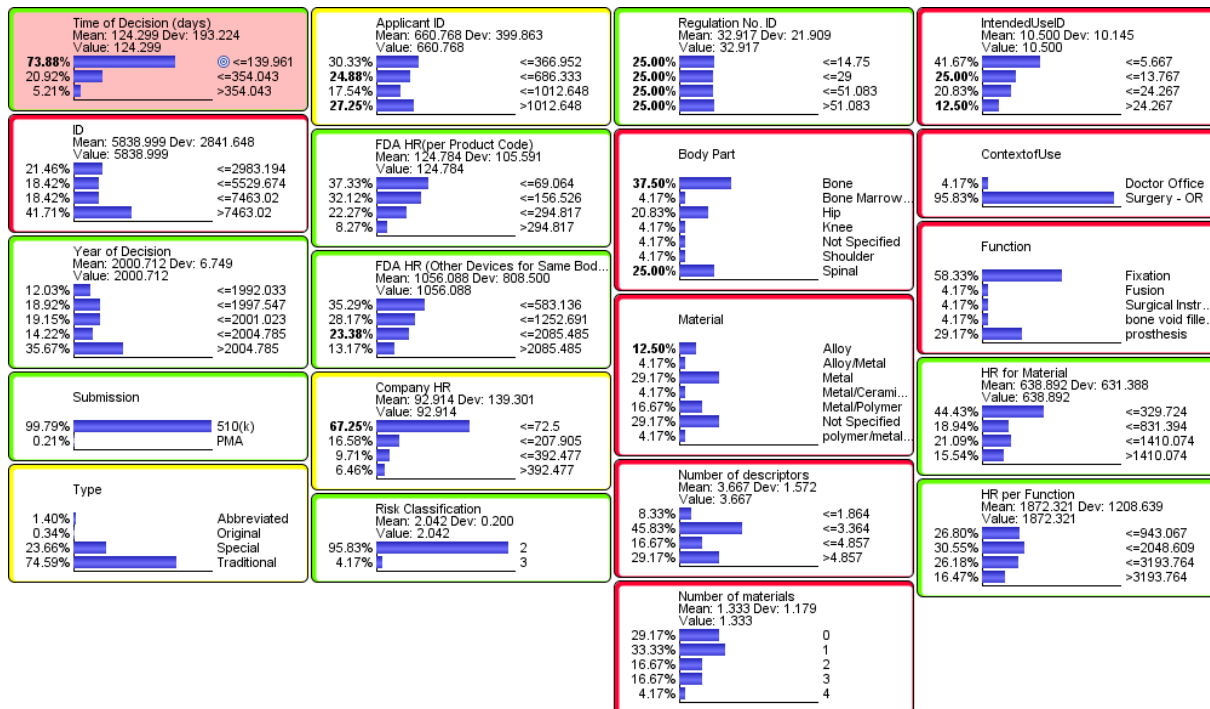

Figure 3. Initial distributions in supervised network

8   CONCLUSIONS

This paper provides a BN approach for the identification of critical factors for MDD. The use of BN provided a more robust analysis of the relationship between variables with the development of a valid network of the product, company and regulatory environment variables in relation with FDA decision time. Some of the relevant variables included the type of submission, year of decision and historical reference. The analysis underlines the necessity of investigating FDA regulatory environment having high constraints on acceptability of devices but also investigations on previous information on materials and Historical references. If this information has been investigated and provided to FDA, the decision time seems to be decreasing. It has also been pointed out that some companies with higher numbers of submissions tend to have greater acceptability of devices, showing the necessity for companies of understanding current FDA regulatory trends as well as medical concerns that have high priority for a given period.

Some of the future research directions may include investigating more the importance of product complexity, submission type and historical reference, along with the interrelations between the different variables.
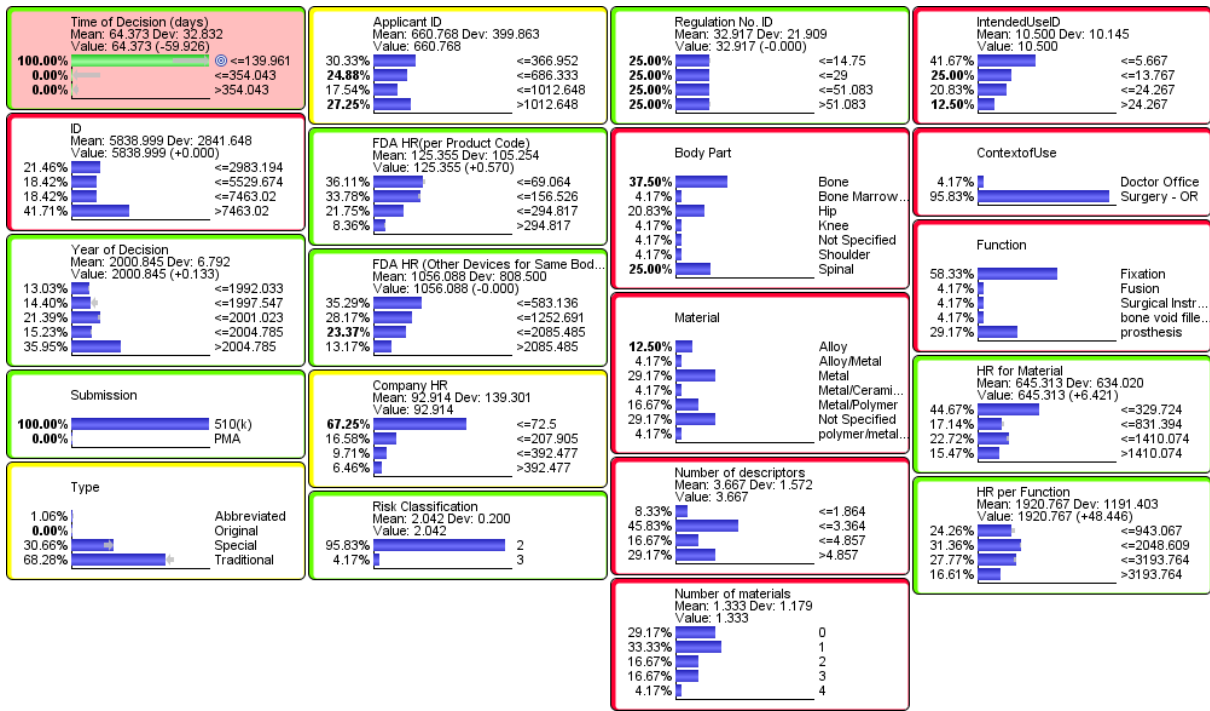
Figure 4. Product Variables for the FDA Decision Time Cluster1 (Decision Time<139.961 days)
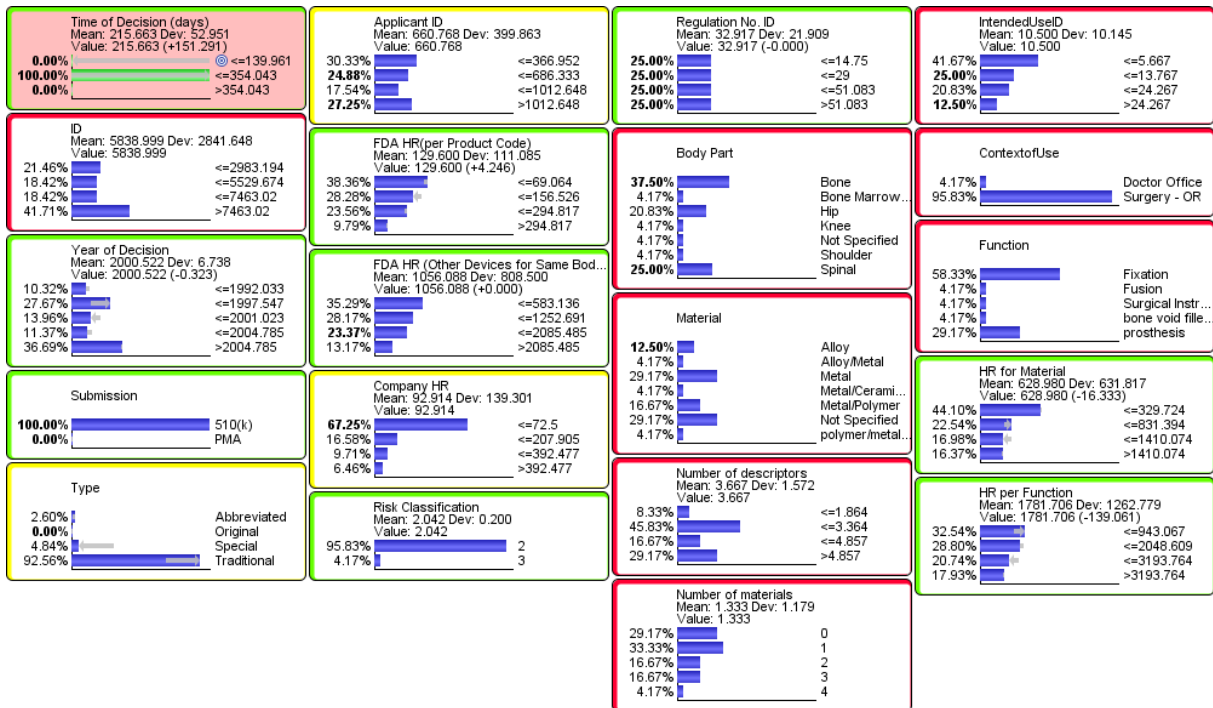

Figure 5. Product Variables for FDA Decision Time Cluster 2 (139.961<Decision Time< 354.043)

Time of Decision (days)
Mean: 607.376 Dev: 610.304
Value: 607.376 (+391.713)
0.00%   <=139.961
0.00%   <=354.043
100.00% >354.043

Applicant ID
Mean: 660.768 Dev: 399.863
Value: 660.768
30.33% <=366.952
24.88% <=686.333
17.54% <=1012.648
27.25% >1012.648

Regulation No. ID
Mean: 32.917 Dev: 21.909
Value: 32.917 (+0.000)
25.00% <=14.75
25.00% <=29
25.00% <=51.083
25.00% >51.083

IntendedUseID
Mean: 10.500 Dev: 10.145
Value: 10.500
41.67% <=5.667
25.00% <=13.767
20.83% <=24.267
12.50% >24.267

ID
Mean: 5838.999 Dev: 2841.648
Value: 5838.999
21.46% <=2983.194
18.42% <=5529.674
18.42% <=7463.02
41.71% >7463.02

FDA HR(per Product Code)
Mean: 97.356 Dev: 80.788
Value: 97.356 (-32.244)
50.53% <=69.064
24.09% <=156.526
24.51% <=294.817
0.87%   >294.817

Body Part
37.50% Bone
4.17%   Bone Marrow...
20.83% Hip
4.17%   Knee
4.17%   Not Specified
4.17%   Shoulder
25.00% Spinal

ContextofUse
4.17%   Doctor Office
95.83% Surgery - OR

Year of Decision
Mean: 1999.588 Dev: 6.015
Value: 1999.588 (-0.934)
4.79%   <=1992.033
47.95% <=1997.547
8.26%   <=2001.023
11.33% <=2004.785
27.67% >2004.785

FDA HR (Other Devices for Same Bod...
Mean: 1056.088 Dev: 808.500
Value: 1056.088
35.29% <=583.136
28.17% <=1252.691
23.38% <=2085.485
13.17% >2085.485

Material
12.50% Alloy
4.17%   Alloy/Metal
29.17% Metal
4.17%   Metal/Cerami...
16.67% Metal/Polymer
29.17% Not Specified
4.17%   polymer/metal...

Function
58.33% Fixation
4.17%   Fusion
4.17%   Surgical Instr...
4.17%   bone void fille..
29.17% prosthesis

Submission
96.00% 510(k)
4.00%   PMA

Company HR
Mean: 92.914 Dev: 139.301
Value: 92.914
67.25% <=72.5
16.58% <=207.905
9.71%   <=392.477
6.46%   >392.477

Number of descriptors
Mean: 3.667 Dev: 1.572
Value: 3.667
8.33%   <=1.864
45.83% <=3.364
16.67% <=4.857
29.17% >4.857

HR for Material
Mean: 587.631 Dev: 587.898
Value: 587.631 (-41.348)
42.31% <=329.724
30.01% <=831.394
14.60% <=1410.074
13.08% >1410.074

Type
1.46%   Abbreviated
6.51%   Original
0.00%   Special
92.04% Traditional

Risk Classification
Mean: 2.042 Dev: 0.200
Value: 2.042
95.83% 2
4.17%   3

Number of materials
Mean: 1.333 Dev: 1.179
Value: 1.333
29.17% 0
33.33% 1
16.67% 2
16.67% 3
4.17%   4

HR per Function
Mean: 1549.066 Dev: 1157.341
Value: 1549.066 (-232.640)
39.65% <=943.067
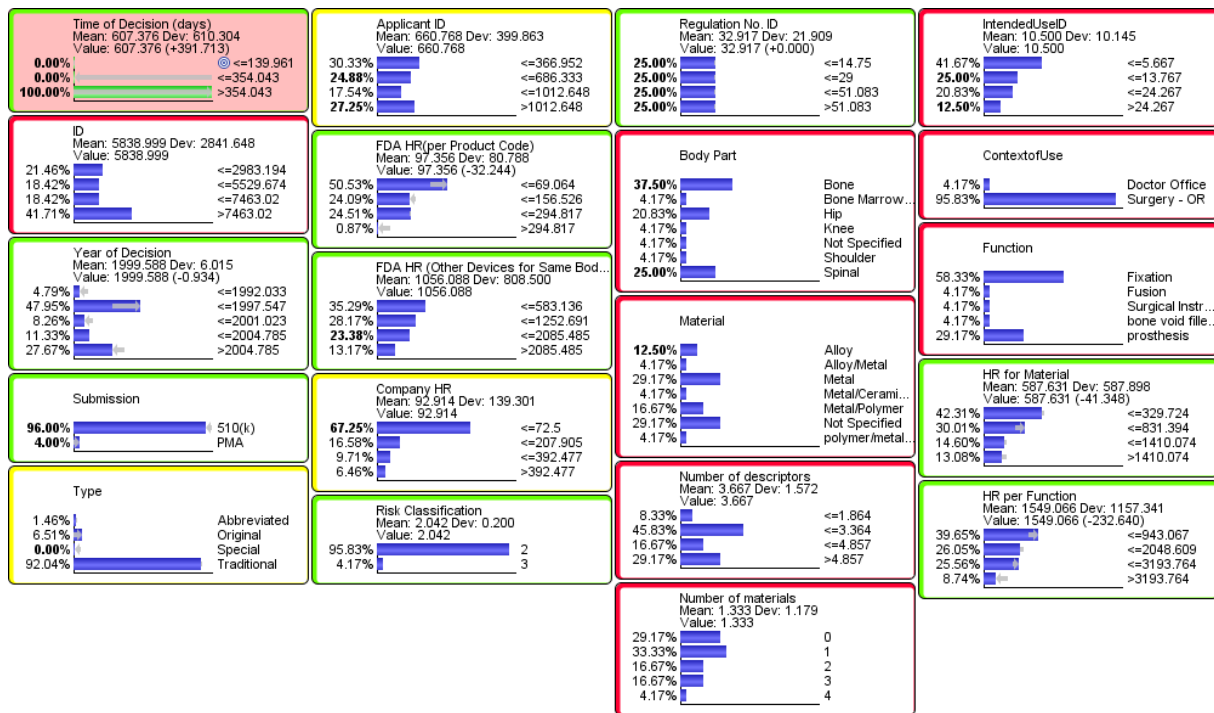26.05% <=2048.609
25.56% <=3193.764
8.74%   >3193.764

Figure 6. Product Variables for FDA Decision Time Cluster 3 (Decision Time>354.043 days)

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ANNEX

Variable Name (number of levels)	Internal or External	Quantitative or Qualitative	Association
FDA's Decision Time	External	Quantitative	Regulatory environment (FDA)
Applicant (474): Company making the submission.	N/A	Qualitative	Company
Submission Year (33, years 1977 - 2010): Year in which the company submitted to FDA.	N/A	Qualitative	Company
Submission Type (2): Submission used for the device: 510(k) and PMA.	External	Qualitative	Regulatory environment (FDA)
Submission Sub-Type (4): Sub-category to further describe the type of submission used: Original for PMAs, and Traditional, Special, or Abbreviated for 510(k).	External	Qualitative	Company
Product Code (24): FDA classification that groups devices with same characteristics and requirements.	External	Qualitative	Product
Risk Classification (2): Represents a classification pre-determined by FDA to group devices based on the level of risk and scrutiny of their regulation. There are 3 classifications, I, II and III. The data sets include class II and III.	External	Qualitative	Product
Regulation No. (16): Classification for devices that provide reference to the Code of Federations (CFR) that applies to the particular device. In comparison to the product code, the regulation number provides a more aggregated classification.	External	Qualitative	Regulatory environment (FDA)
Material (7): Specifies the material of the device or a device component (e.g. metal, alloy).	Internal	Qualitative	Product
Intended Use (9): Describes the intended use of the product in terms of the clinical need.	Internal	Qualitative	Product
Context of Use (2): Explains the setting in which the device is used: surgery- operating room or at the doctor's office.	Internal	Qualitative	Product
Body Part (7): Refers to the body part where the device is implemented.	Internal	Qualitative	Product
Function (5): Represents the function of the device.	Internal	Qualitative	Product
Number of Descriptors: Amount of descriptors used for the device's product code.	External	Qualitative	Product
Number of Materials: Amount of materials described for the device's product code.	Internal	Qualitative	Product
FDA Historical Reference per Product Code: Number of devices previously approved by FDA with same product code.	External	Quantitative	Regulatory environment (FDA)
Company Historical Reference: Number of submissions previously done by the same company (independent of being 510(k) or PMA)	External	Quantitative	Company
Historical Reference per Body Part: Number of devices previously approved by FDA for the same body part.	External	Quantitative	Regulatory environment (FDA)
Historical Reference per Function: Number of devices previously approved by FDA for the same function.	External	Quantitative	Regulatory environment (FDA)
Historical Reference for Material: Number of devices previously approved by FDA with the same other descriptor.	External	Quantitative	Regulatory environment (FDA)