Modeling of the FDA Approval Process: Connections between Financial Risk, Early Decision Making and Future Pricing

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ABSTRACT

This paper discusses the planning of the different steps associated to projects featuring high risk/high return characteristics, which require FDA approval. We present a model that connects early decision making, such as level and intensity of pre-testing or investment on facilities, among others, with the FDA approval process and the final commercialization step, which include pricing, advertisement and other marketing instruments. The model is probabilistic. Moreover, we use conditional probabilities relating probabilities of events to prior history. The stochastic nature of the model allows risk management. We illustrate the concepts with a skin allograft product. Additional examples will be shown in the presentation.

Introduction

The FDA approval process for new drugs and medical devices/products can take years and it requires spending a large amount of resources. The process is usually preceded by some in-house pre-application testing that also requires time and resources. If one minimizes the pre-application testing to a few tests, then one reduces the total time to market, but also increases the chances of failure during the FDA approval period. Fixing these failures during the FDA is typically more costly and may require more time than fixing them in the pre-approval testing period. This may even result in a longer total time to market. Making the right decisions on the level of testing before starting the FDA approval is therefore important. To allow proper decision making, we have constructed a decision based pert with dynamic allocation of probabilities based on prior events. By simple enumeration of all possible paths we are able to link decisions related to the pre-approval testing to the expected cost of the FDA process, which is also in turn associated to the expected time to market. It is also possible to assess the probability of success.

In addition, pricing of the future product, years from now in a virgin market or in one where there will be competition is also a matter of consideration. It helps decide, together with the chances of passing the FDA approval, whether the expected profit given success in the FDA approval, is justified by the appropriate level of risk. We will illustrate how these pricing decisions affect the decision making.

Skin Replacement Case Study

In 1980, Yannas and Burke developed a bilayered dermal regeneration template using primarily refined collagen from bovine tendons cross-linked with chondroiten 6-sulfate from shark cartilage. We have performed the design of a new product, which improves the design of Yannas and Burke by releasing an angiogenesis-stimulating growth factor (VEGF) that effectively shortens the vascularization healing time. The equipment needed to fabricate 6000 6"x 4" sheets per month requires an investment of around $110,000 and has a cost of $195/sheet not including labor costs, which are as large as 6 million/year, but are lower during the first year. The facility required includes cryogenic, reproduction, product storage, animal storage, laboratory and administration rooms, amounting to 30,000 sqft at an estimated cost of $8.25 million dollars.

Since the product is a medical device, it will go through the Center of Devices and Radiological Health (CDRH). Under the CDRH, devices are further classified into class I, II and III devices. The product falls under the class III devices. The FDA requires that all class III devices go though a process known as the Pre-market Approval process (PMA). The PMA is a scientific and regulatory review to evaluate the safety and effectiveness of the device; it is the first step in the process that will eventually lead to FDA approval. The whole process can take anywhere from 10-15 years and for this case 2 years of pre-testing are considered prudent.

Including delays, the PMA application review process can take between six and twelve months. The cost of the PMA process is between $50,000 and $60,000 plus an application fee of PMA application is $206,811. There are two ways to file for PMA application: by Modular PMA (1) or Traditional PMA (2). For this study we have chosen the modular PMA route, which has 3 modules:

1. Module 1 Non-clinical laboratory studies phase 1 (cellular) and phase 2 (animal) testing
2. Module 2 Manufacturing Information module
3. Module 3 Final PMA (human clinical studies) module

Pre-FDA Testing and related decisions

Three different workforce sizes were considered: 1 Ph.D. with 3 lab technicians, 1 Ph.D. with 5 lab technicians, and 1 Ph.D. with 7 lab technicians, with a pre-FDA approval cost of $205,000/yr, $275,000/yr and $345,000/yr. With more lab technicians, one is able to bring a product to the FDA quicker, run more tests in order to have a better chance of passing the FDA on the first try, and be able to start selling products on the market quicker. We assume here that initial funding will come from granting agencies, such as the National Institute of Health, National Science Foundation, and the Center for Disease Control. Thus, the size of the team, and consequently, the number of experiments that can be run are contingent to the funding secured. Since this is the first step (non securing this funding) stops the whole process, we will analyze the case study for all three possibilities. The number of experiments that will be run in each case will vary. We have classified these as set A, B and C, and these are in fact our first stage decisions (Figure 1). The following experiments are considered: Cellular level flask tests, Chorioallantoic Membrane (CAM) Tests, Nude Mice Burn Treatment, Diabetic Guinea Pigs, Pigs, Diabetic Dogs. The number of such experiments is depicted in Table 1.

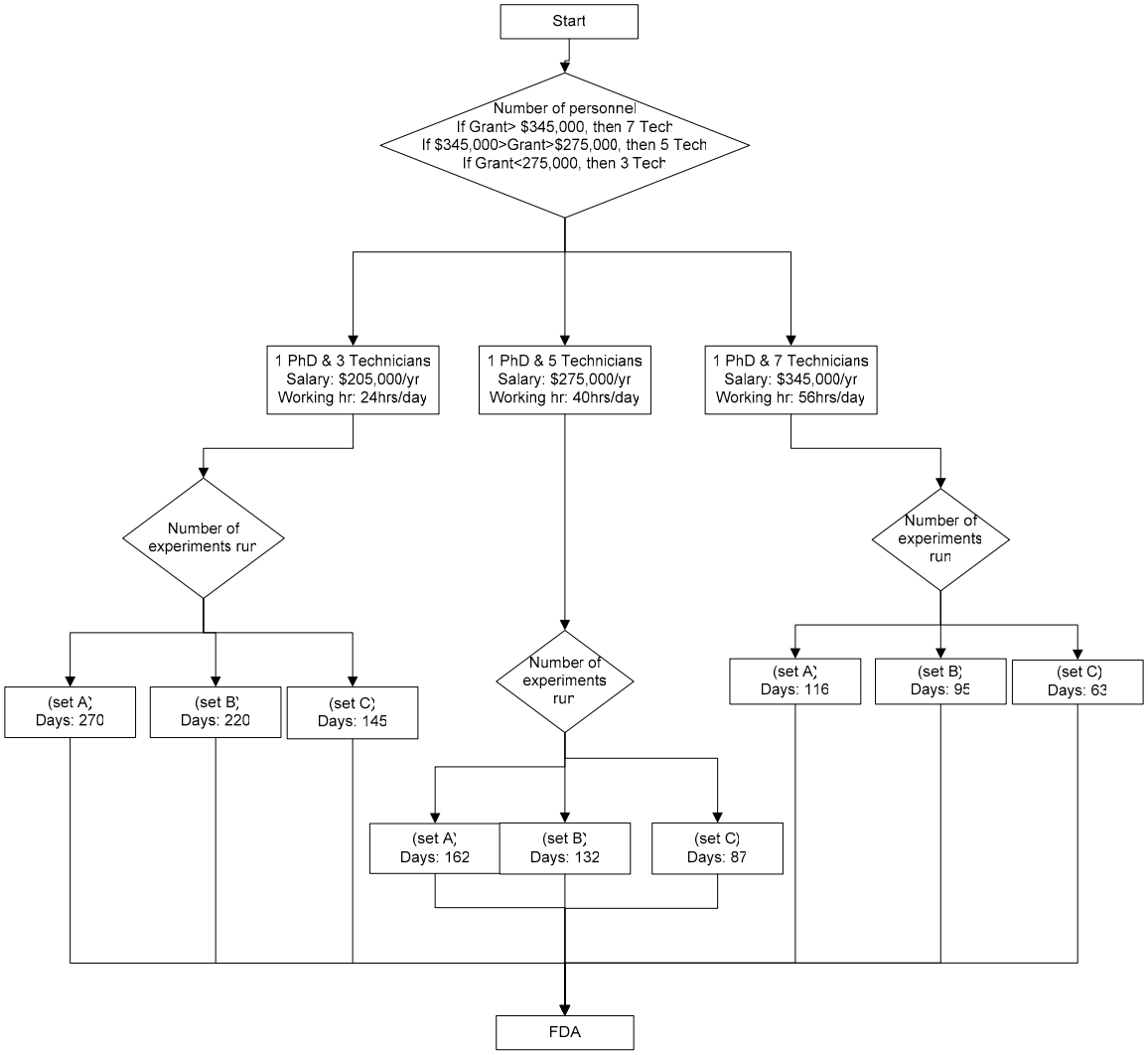

Figure 1. Options and First stage decisions for Pre-FDA Testing.

Table 1. Number of Successful Tests Run in Each Pre-FDA Testing Set

	Number of Cell-Flask Tests	Number of CAM Tests	Number of Nude Mice Tests	Number of Diabetic Guinea Pig Tests	Number of Pig Burn Tests	Number of Diabetic Dog Tests
Set A	100	100	100	100	100	100
Set B	100	100	50	50	50	50
Set C	50	50	50	50	25	25

FDA process

In Module 1, the first phase consists of non-clinical laboratory testing involving chemical testing, biocompatibility or toxicity testing and animal and biological testing. In addition, sterilization, shelf life and packaging are tested. The time for these tests is about 2 years. The second phase consists of determining compatibility with small living animals (mice). The third phase tests the interaction of the dermal replacement sheets with large animals (pigs and dogs).

Module 2 involves detailed manufacturing information of the product. The FDA requires that domestic or foreign manufacturers have a quality system for the design, manufacture, packaging, labeling, storage, installation, and servicing of finished medical devices intended for commercial distribution in the United States. Some regulations have therefore been set up by FDA known as Good Manufacturing Practices (GMP) or Quality System (QS) Regulations. The following needs to be considered:

- The production processes should be developed, conducted, controlled, and monitored to ensure that a device conforms to its specifications.
- Management need to provide adequate resources like trained personnel, review the sustainability and effectiveness of the quality systems frequently.
- Inspection control requires that equipments be measured, tested calibrated and maintained routinely.
- Device packaging, storage and labeling should be appropriate.

Module 3 involves Clinical trials. This is the final module in which all the clinical data, financial disclosure information, instruction for surgeons, and operation manual is completed. This is not only the most expensive phase, but it is also the longest phase in the PMA approval process. It took 17 years for a skin replacement product that is already in the market to go through clinical trials. Since the new product under analysis has similarities the estimate is that it will take about 10 years to go though clinical trials. This time frame assumes that all of the trials are successful on the first try. It was assumed that clinical trials will be preformed using 900 patients over this period: 450 Burn patients and 450 Diabetic Ulcer patients. The FDA randomly selects the hospitals. The cost to perform clinical trial studies per patient was averagely estimated to be $760,000 per burn patient and $20,000 per diabetic ulcer patient. Adding the cost of personnel and production the total cost of this phase is around $351,000,000**.**

Modeling: For each of the modules, we have constructed a flowchart diagram like the one shown in Figure 2 for Module 1. Potential failures and their solutions have been determined and incorporated in this flowchart. In addition, for each failure the probability has been computed and the cost of the procedure to fix the problem was determined. For example, in figure 2, we have the probability of success the first time around to be 70%, and the probabilities of the three possible failures to be 10% each. Finally, the time required for each task to perform was computed. In many cases, the probabilities of failures have been made a function of prior decision making. For example, module 1 testing has a 70% probability of approval the first time, whereas pursuing the testing a second time has a 90% probability of approval. Similarly, if a decision to run one hundred experiments with 7 technicians is made, the probability of approval at the same level is higher than the situation where fifty experiments are done with 3 technicians.

Once the flowcharts are constructed, the different possible paths were determined. Paths are a sequence of events that either lead to abandoning the project or to the next module. For example, failure of module 1 testing due to the number of microbeads leads to the decision of whether or not to continue. Continuing leads to modifying the number of microbeads at a cost of and a period of time and the path is still active, whereas discontinuing leads to scrap which is the termination of the path. Finally, the probability of each path is computed by multiplying the probabilities of all the failure nodes that the path contains.

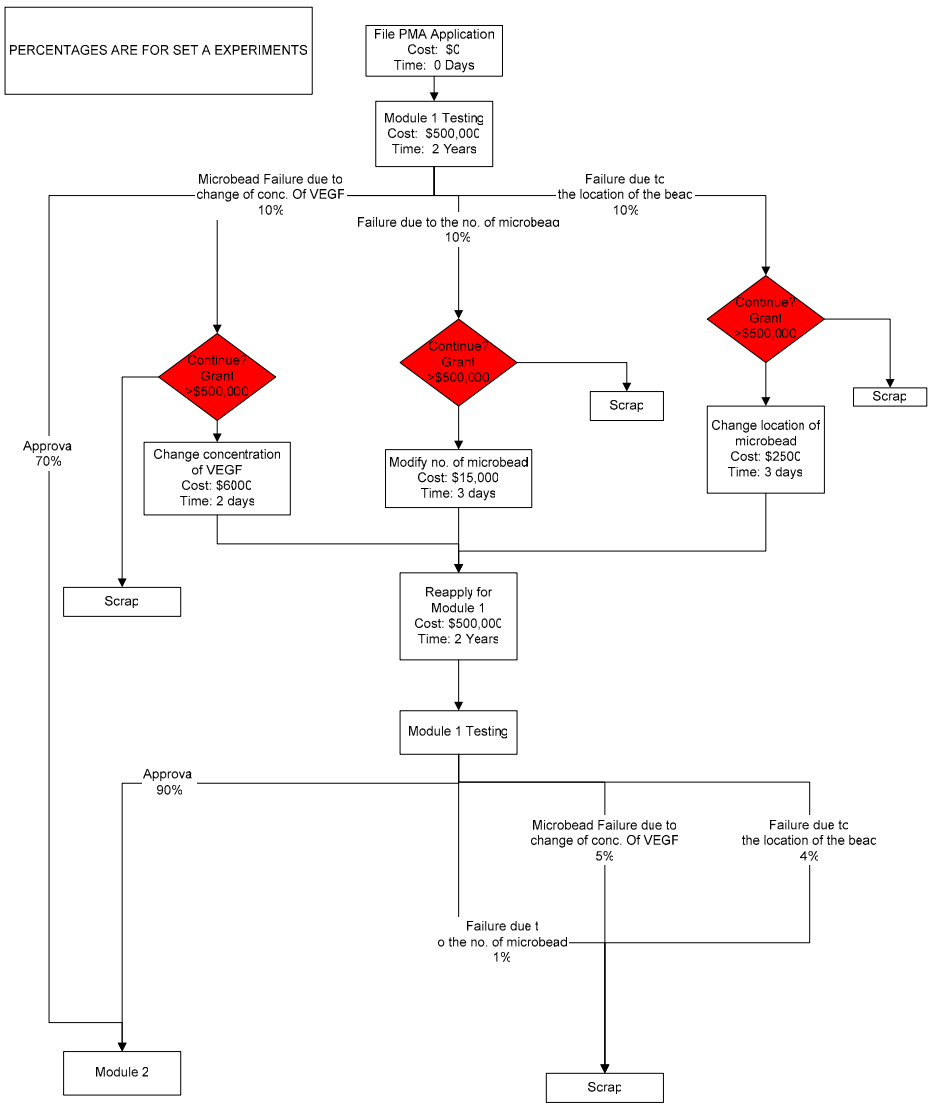

Figure 2. Module 1 Paths. Skin Replacement Case Study.

Decision Making

There are several concerns. Some are summarized next:

- Which of all the tests that could be made should be made in the pre-testing phase?
- How many technicians and professionals need to be hired and when?
- When to start the building of production facilities? What is the production capacity to target before commercialization
- What is the selling price that the new product will have?
- What is the level of advertising and the market penetration strategy?
- When and what capacity of expansions need to be planned?

The main trade offs that the answers to the above questions resolve are:

- The more tests are made in the Pre-FDA phase, the more personnel needs to be hired, which increases costs, but may speed up the FDA approval phase afterwards and therefore reduce the time to market.
- The largest the capacity of the production facility, that is built during (or even before) the FDA approval period, the largest the cost, but also the largest potential sales.

However, one of the important factors of all this process is that everything is uncertain, and no matter how good forecasting tools one possesses, such uncertainty cannot be reduced to zero. These uncertainties are:

- Pre-FDA and FDA tests may fail, and repetition of them increases time to market, or may even drive the project to be abandoned.
- Market demand and prices, especially years down the road, are fuzzy.
- The response of the customers to advertisement efforts may not be the anticipated one.

Thus, one is faced with a long list of decisions that need to be made, some of them early on and some at some later stage, which are based on uncertain data. While waiting for a later time to make a decision is advantageous and one should do that almost always because there is always more data to use to make such decision, knowing what are the possible choices one will be facing in the future and the likelihood of different outcomes is vital to shape up the decisions that need to be made now. In the next sub-section we review how this decision making process can be framed in the context of Two-stage stochastic modeling techniques.

Two Stage Stochastic Modeling

These types of models assume that some decisions are taken at the planning stage, that is, before the uncertainty is revealed, while other decisions can only be made afterwards. The former are called *first-stage decisions*. The decisions made after the uncertainty is unveiled are called *second-stage* or *recourse decisions*. In most cases, first stage decisions are related to capital investment at the beginning of the project, while the second-stage decisions are most of the time operational. Yet, some structural decisions corresponding to a future time can be considered as a second-stage, that is, one will wait until some uncertainty (not necessarily all) is unveiled to make these additional structural decisions. Among the two-stage stochastic models, the expected value of the cost (or profit) resulting from optimally adapting the plan according to the realizations of uncertain parameters is referred to as the *recourse function*. We will consider here the class of problems in which for every feasible first-stage decision, there is always way of adapting the plan to the realization of uncertain parameters. For our problem, we classify our variables as follows:

- First Stage (x): Number and nature of pre-FDA tests to make and personnel to hire.
- Second Stage (y): Decisions to abandon the project, Size and Timing of production facility, Pricing and Market strategy.

Options Evaluation Procedure

While there are mathematical programming methods that help model the decision making process (Birge and Louveaux, 1997), we seek here a less programming oriented strategy:

- We first list the options for each of the first stage decisions, and
- We evaluate the cost of the pre-testing process for each set of first stage decisions
- We evaluate the outcome of the FDA approval for each of these sets by tracing all the possible paths of the FDA process. The paths have a cost and a time associated to them.
    - Each of the steps of any path of the FDA process has a probability associated to it. Therefore, each path has a probability.
    - The sum of the time or cost corresponding over all paths multiplied by their probability allows the calculation of the expected time consumed by the FDA

approval process or the expected cost. This is also illustrated below.

- Finally, we develop a model to determine the price and we evaluate the profit obtained from the commercialization step.
- The expected profit for each option is calculated and the financial risks for all options are compared. This is discussed in more detail below.

Uncertainty Model and Financial Risk

The above FDA and commercialization model provides the means to build a histogram of profit. Consider as an example six paths corresponding to a set of first stage decisions. Assume 3 paths are leading to abandoning the project and 3 are successful. Since the probabilities, profits and costs of each of these paths are different, we plot the histogram of profit in Figure 3. In addition, one might add the uncertainties corresponding to demands, prices, fixed capital and operating costs (including labor). In Figure 4 the corresponding cumulative profit distribution, also known as financial risk curve (Barbaro and Bagajewicz, 2004) is shown.

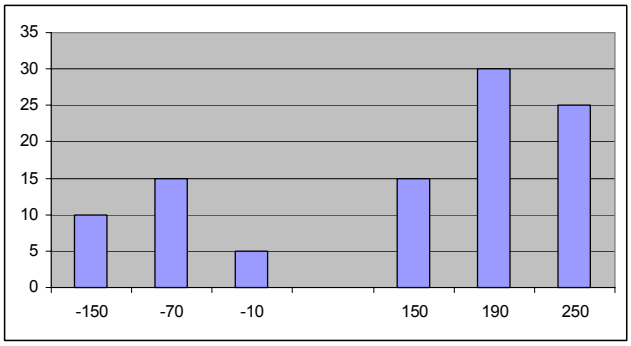

Figure 3. Generic Profit histogram.

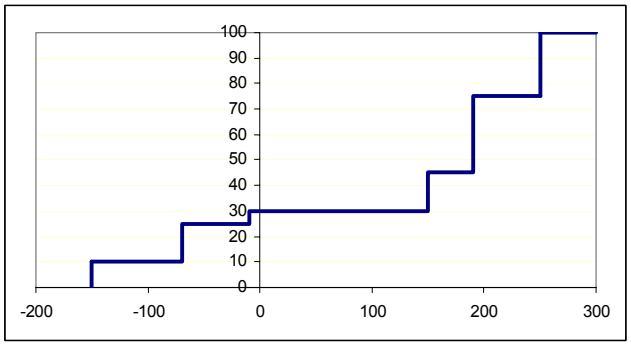

Figure 4. Generic Risk Curve.

Clearly, different choices of first stage variables lead to different risk curves. This situation is illustrated in Figure 5. Plan I has a larger expected profit (120.5 vs. 68.05). However, a closer look at the distribution shows that Plan I carries a much higher risk. Indeed, the probability of loosing money, given by the risk at the target profit of zero is 30%, while that of Plan II is only 20%. Moreover the downside risk at profit zero is -$2,150 and -$1,295 respectively. A strongly risk averse investor will always prefer plan II, while a risk taker will prefer plan I.

Results

The estimated demand *D* was obtained from current production of one company in the market, (100,000 dermal replacement sheets per year). Since this company holds 20% of the total market, the total market is approximately 500,000 sheets. The current price of $1000/sheet. Our cost is $195/sheet. We performed full simulations to evaluate the different paths of each alternative and obtained the risk curves. Figure 6 shows preliminary results corresponding to three risk curves constructed for the case of 1 Ph.D. and 3 Technicians. The risk curves for the other two alternatives are similar. We are revising and completing all the calculations. We will discuss these and many other results during our presentation, including the effect of pricing.

Conclusions

We have presented a methodology that allows the modeling of the FDA approval process and the assessment/management of the risk. The methodology allows comparisons of different early decisions. We will illustrate several different cases during our presentations.

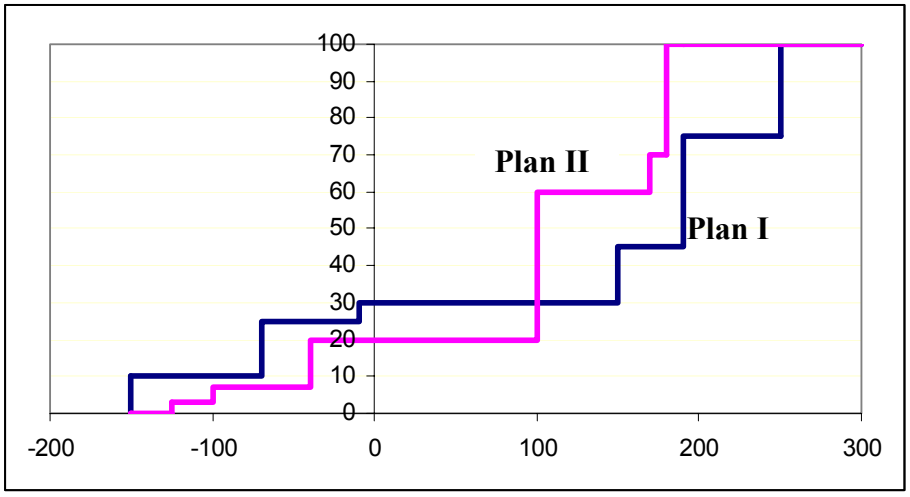

Figure 5. Comparison of Risk Curves.

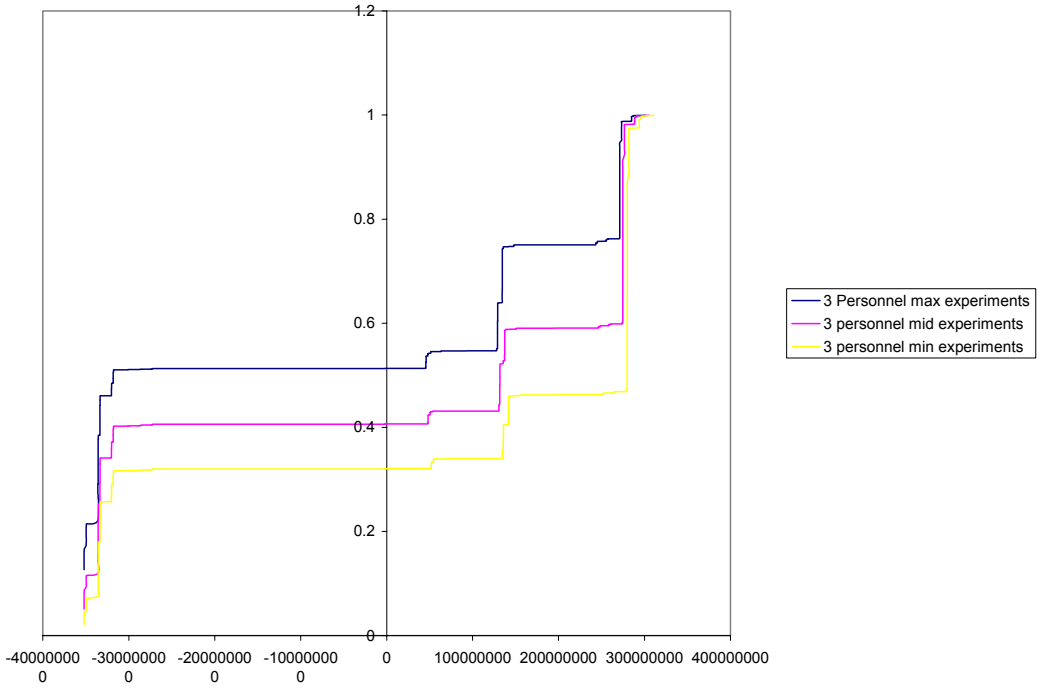

Figure 6. Risk Curves for all experiment sets with 1 Ph.D. and 3 Technicians

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