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ABSTRACT

The rapidly changing biomedical device industry and the associated pace of the advancement of technology requires that biomedical device companies release products into the marketplace as fast as possible to recoup the investment made into them as well as to cope with fierce competition. An extensive literature review was performed to discuss the challenging areas in the product and process development of biomedical devices. These included the integration of advanced technologies, the integration of biomedical devices with the human body, government regulations, biomedical product liability issues, social and ethical issues, as well as sterilization methods. This research proposed that the use of computer simulation, in particular, SLAM II, can help biomanufacturing companies incorporate planned flexibility and strategic planning in product and process development, while addressing the challenges in the field of biomanufacturing.

Although a well-planned process development can ensure rapid time-to-market and a more solid proprietary position for biomanufacturers, no research was found that investigated the use of simulation as a project management tool to accelerate biomedical device product and process development and to estimate the risks involved in the decision-making process. Therefore, this thesis addressed two important objectives in biomedical device project planning: minimizing project completion time and the associated risks.

This research was concerned with the development of a methodology for creating product and process development plans using simulation technology. The Biomedical

Operations Project Planning (BOPP) methodology was developed to aid project planners in the creation of biomedical device product and process development simulation models. The general biomedical device product and process development simulation model consists of 14 steps, from the development of the model to the analysis of the results. Several combinations of nodes and activities (subnetworks) within SLAM II were created to facilitate the use of simulation in the project planning of biomedical devices. This research also developed necessary data collection and general biomedical device simulation model templates, thereby providing project planners with the option of either modifying the templates to suit the needs of different medical devices or developing new simulation models using the instructions in the BOPP methodology.

Finally, a model of product and process development of an external insulin pump is provided as an example application of the BOPP methodology.

CHAPTER 1

INTRODUCTION

The field of biotechnology has come a long way since early antiquity when the Chinese used moldy soybean curds as an antibiotic to treat boils and when the Greeks practiced crop rotation to maximize soil fertility. Over the past few decades, new biotechnological developments have been made in the areas of healthcare, agricultural, and chemical or energy industries that greatly enhanced our quality of life.

The biotechnology industry is a strong economic force. Total revenues for biotechnology companies increased from $17.4 billion in 1998 to $18.6 billion in 1999 (Ernst & Young LLP, 1999). Table 1 shows biotechnology industry statistics from 1993 to 1999 on sales, revenues, research and development (R & D) expenses, number of companies, and number of employees. The total number of biotechnology product patents granted from 1985 to 1998 is shown in Figure 1 (Biotechnology, 1999). The upward growth in the number of patents that were granted further confirms the strength of the biotechnology industry.

Table 1: Biotechnology Industry Statistics.

Year	1993	1994	1995	1996	1997	1998	1999
Sales*	5.9	7.0	7.7	9.3	10.8	13.0	13.4
Revenues*	8.1	10.0	11.2	12.7	14.6	17.4	18.6
R & D Expenses*	4.9	5.7	7.0	7.7	7.9	9.0	9.9
Number of Companies	1231	1272	1311	1308	1287	1274	1283
Number of Employees	79,000	97,000	103,000	108,000	118,000	141,000	153,000

*US$ billions

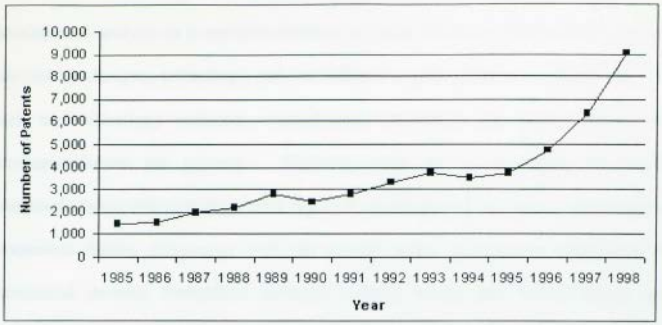

Figure 1: Total Biotechnology Product Patents Granted Per Year.

As the medical technology industry grows, it requires timely transfer of concepts from research and development to product manufacturing. For a biomedical device or pharmaceutical manufacturer to remain on the competitive edge, not only is it necessary to satisfy the stringent demands of the biotechnology markets, but also to develop processes that can accelerate the time from research and development to manufacturing and actual marketing of the medical products.

The medical device industry has become one of the strongest sectors in the U.S. economy. This industry manufactures a wide range of products, from medical disposables to highly sophisticated diagnostic systems. The term "biomedical device" is used to define medical devices that are integrated into or interactive with human systems, such as pacemakers, implantable cardioverter defibrillators, and implantable insulin pumps. Biomanufacturing has been defined as "the design, development, implementation, and management of systems for the production of products that are integrated into or interactive with human systems" (Grant, 1999).

Biomanufacturing is a potentially important area for product and process development analysis as it typically involves products that are expensive and complex, use rapidly changing technology, and are difficult to manufacture on a large-scale. In such high-technology industries, technological innovation and speed-to-market are dominant factors for survival. However, there are many factors that make biomanufacturing different from other types of manufacturing such as the importance of biomedical device integration with the human body, government regulations on biomedical devices, biomedical products liability, social and ethical issues, and sterilization processes. These unique characteristics of biomanufacturing make it even more challenging for product and process planning.

A lot of focus has also been placed on simultaneous engineering methods and on product and process cycles in order to shorten development times for general products. The product and process development time is extremely critical in the manufacture of high technology biomedical products due to the many processes and regulations involved as well as the extreme competition in the biomedical industry. Therefore, it is essential that new methods be used in biomanufacturing to manage the development and manufacture of these devices.

This thesis explored the use of simulation as a project planning tool to support biomedical device product and process development. The following chapter provides a literature review of biomanufacturing, the product development process, project management, and the use of simulation as a tool for project planning, scheduling, and control. Chapter 3 reviews the problems faced in the biomedical industry with regard to product and process development, with a focus on biomedical device manufacturing.

Chapter 3 also provides the objectives and scope of this research. Chapter 4 discusses Biomedical Operations Project Planning (BOPP). The BOPP is a methodology that was developed to show the application of simulation to the project planning of biomedical devices. The chapter also discusses simulation subnetworks that were created to facilitate the use of simulation for biomedical device project planning. To aid project planners, it also provides templates for data collection and a general biomedical device simulation network model that can be modified and used to fit the needs of unique biomedical devices. Chapter 5 provides an example application of the BOPP methodology in managing the process development and manufacturing of an insulin pump. Chapter 6 provides the summary and conclusions of this research as well as recommendations for future research in the use of simulation in biomedical device manufacturing.

CHAPTER 2

LITERATURE REVIEW

This chapter first provides a background on biomanufacturing in Section 2.1. Section 2.1.1 describes existing biomedical device manufacturing technologies. Section 2.1.2 discusses the issues related to biomedical device integration with the human body. Section 2.1.3 provides information on government regulations on biomedical devices. Section 2.1.4 reviews biomedical product liability. Section 2.1.5 covers social and ethical issues related to the development and manufacturing of biomedical products. Section 2.1.6 discusses the importance of sterilization in biomedical devices.

Section 2.2 reviews the product development process. Section 2.3 explains project management on a broad scope. Section 2.3.1, 2.3.2, and 2.3.3 examine the elements of project planning, scheduling, and control. Section 2.4 discusses the use of simulation in general manufacturing. Section 2.4.1 provides details on the use of simulation as a tool for project planning, scheduling, and control. Finally, Section 2.4.2 provides examples of computer simulation languages in existence today, with a focus on SLAM II.

2.1 Problem Background

Some of the processes used to manufacture biomedical devices and drugs employ similar combinations of standard operating procedures used to manufacture other products. However, there are many issues related to biomanufacturing that distinguish it from the manufacture of other products. The field of biomanufacturing is unique in terms of biomedical device manufacturing technologies, biomedical device integration with the

human body, government regulations on biomedical devices, biomedical product liability, social and ethical issues, and sterilization (Grant, 1999).

2.1.1 Biomedical Device Manufacturing Technologies

Management of technologies in new product development (NPD) processes is a concern of NPD companies and researchers (Scott, 2000). Scott investigated the importance of 24 technology management issues that contribute to decreased effectiveness of NPD projects for high technology products. An initial set of technology management problems was developed based on the literature and the author's experiences. Using the DELPHI Questionnaire Management Issues Methodology, three questionnaires were distributed to the participants requesting them to rank the importance of the problems and provide additional problems that were not included. The top ranked 34 of the original 59 issues were included in the second questionnaire and the top ranked 24 issues out of these 34 issues were used in the third questionnaire. Any additional issues provided in the first questionnaire were added to the second questionnaire and likewise for the third questionnaire.

The results of Scott's study showed that strategic planning for technology products was the most important issue. This category included problems with strategic and long-range planning for technology-product development, such as aligning high technology strategies with business strategies (or vice versa if the technology strategy should be dominant), new product introduction strategies, strategic decision-making processes, lack of understanding of technology and its roles among corporate strategic planners, lack of coherent corporate level planning for high technology management, failure to identify the critical success factors of a company's technology activities, and

establishing the corporation's technology climate. Since biomedical device manufacturing is high-technology manufacturing, it is important for a company to form strategic plans to manage the technology of medical devices.

Some of the technologies that have been integrated in biomedical device manufacturing include Computer-Aided Design and Computer-Aided Manufacture (CAD/CAM) techniques. For example, new horizons have been created in the prosthetic field. In CAD, a prosthetic product is geometrically modeled in three dimensions using a computer so that it can be viewed and examined from all directions. One of the advantages of using CAD is that it provides the designer the opportunity to experiment with design changes to the model, see the results, and analyze the appropriateness of those changes. Such models can be utilized for many other applications, such as manufacturing analysis. In CAM, numerically controlled machining processes can also be used for cutting out prosthetic devices. With this method, geometrical data taken from the CAD model are combined with machining parameters to produce the appropriate machining or cutting tool paths. This information can then be analyzed by graphic simulation to verify the process (Bok et al., 1990).

Gupta and Wilemon (1996) studied Research and Development directors involved in research and development management and new product development efforts. The directors worked in 120 technology-based manufacturing firms consisting of chemical, electrical, electronics, information processing, telecommunications, instrumentation and control, and semiconductor industries. By distributing questionnaires comprised of several structured questions as well as a limited number of open-ended questions, they discovered that most of the directors agreed that open, frequent, and early communication

with customers and stakeholders in areas such as research and development, marketing, manufacturing is the key to successful new product development. The results also showed that a majority of the companies use CAD, simulation tools, and other software to make their product development more efficient.

Advanced technologies in micromachining, due to increased interest in the development of microelectromechanical systems (MEMS), can also create dilemmas in manufacturing. Microdevices are usually measured in terms of micrometers and are usually invisible to the naked eye. The manufacturing of these devices can cause unique problems. For example, factors such as vibration and gravity, that affect the operations of other manufactured products such as gear assemblies, do not affect microdevices. Instead, microdevices are affected by other problems such as stiction, that is, the tendency of these devices to stick to one another. Examples of microdevices that are currently undergoing research at Ohio State University are silicon microcapsules (Nighswonger, 1999). These microcapsules are about the size of pinheads. They are implanted just below a patient's skin with the capability of carrying healthy transplant cells to replace the patient's malfunctioning cells and produce needed chemicals for the body. Microinstruments are also being developed for endoscopic procedures. These microdevices present many manufacturing challenges as product developers are working on adding more advanced endoscopic functions while maintaining the same micro-dimensions.

2.1.2 Biomedical Device Integration with the Human Body

Another issue important to product developers and manufacturers of biomedical devices is the integration of biomedical devices with the human body. Medical devices

are governed by the International Organization for Standardization (ISO) standard 10093-1, which states that "in the selection of materials to be used in device manufacture, the first consideration should be fitness for purpose having regard to the characteristics and properties of the material, which include chemical, toxicological, physical, electrical, morphological, and mechanical properties." The document also states that "the following should be considered for their relevance to the overall biological evaluation of the device: a) the material(s) of manufacture; b) intended additives, process contaminants and residues; c) leachable substances; d) degradation products; e) other components and their interactions in the final product; and f) the properties and characteristics of the final product" (Albert & Wallin, 1998).

Medical device designers currently have limited types of materials to develop their products. Table 2 illustrates some of these materials (Kohn, 1996). However, new research in biomaterials aimed at creating scientific breakthroughs in the understanding of cell-materials interactions can lead to improvements in disease treatment.

Table 2: Materials Commonly Used in the Manufacture of Medical Implants and Devices.

Type of Material	Specific Examples
Biostable polymers and resins	Polyurethanes, silicone rubber, Teflon®, Dacron®, nylon, polymethylmethacrylate (PMMA)
Biodegradable polymers	Poly(lactic acid), poly(glycolic acid), polydioxanone
Natural and semi-synthetic products	Treated porcine grafts, bovine pericardium, processed cellulose, processed collagen
Metals	316 and 316L stainless steel, Vitalium®, titanium alloys, Co-Cr-Mo alloy
Ceramics	Aluminum oxides, calcium aluminates, titanium oxides, pyrolytic carbon, Bioglass®, hydroxyapatite
Composites	Apatite composites, carbon coated metals, carbon reinforced polymers

Plastics are also commonly used in medical devices. They may be classified into five groups as shown in Table 3 (Leuschner & Rimpler, 1990). Although plastics are useful for medical devices, they can also cause problems such as chemical reactivity, leachability, migration, biodegradation and mechanical abrasion. Plastics have the tendency to react chemically with the surrounding tissue and body fluids. The leaching of material or ingredients from the plastics may also cause local or systemic toxicity. Due to its dependency of shape and its passiveness, the host may try to rid itself of the implant causing migration of the product. Whether desired or undesired, degradation of plastics is also of concern as well as the metabolic alteration of the plastic by the surrounding tissue. Plastics also pose problems in terms of abrasion and systemic deposition of the particles (Leuschner & Rimpler, 1990). Therefore, product developers and manufacturers need to be aware of these problems when developing biomedical devices to be integrated with the human body.

Table 3: Plastic Medical Device Classification.

Group	Examples
Permanent Implants	Vascular grafts, hip prostheses, other artificial organs, pacemakers
Materials in contact with mucosal surfaces or with the conjunctivae	Artificial eyes, contact lenses, dentures, intrauterine devices, catheters
Materials in contact with skin	Splints, braces, films, protective clothes
Collection and administrative devices	Blood transfusion sets, disposable syringes, cannulas, catheters, tubing, dialyzing units
Storage devices	Containers, bags for blood, blood products, diagnostic agents

2.1.3 Government Regulations

The U.S. Food, Drug, and Cosmetic Act requires that all devices for human use be classified by the Food and Drug Administration (FDA) into one of three regulatory

classes so that each device will be subject to controls that are appropriate for that type of device (FDA, 2000). Class I applies to medical devices under General Controls. This requires the registration of manufacturers, record-keeping, labeling, and Good Manufacturing Practice (GMP). Class II applies to medical devices under Performance Standards. Medical devices in this class not only need to satisfy the requirements of General Controls, but must also meet performance standards in terms of materials, construction, components, and properties. Class I and Class II medical devices usually require the submission of Premarket Notification (PMN) before being marketed. Finally, Class III applies to all medical devices that need Premarket Approval (PMA). These medical devices need to be pre-approved by the FDA for safety and effectiveness. A majority of these medical devices are implanted and are life supporting or sustaining devices. Many Class III devices present a potential unreasonable risk of illness or injury. The focus of the current research is on biomedical devices within Class I and Class II that require PMN.

2.1.4 Biomedical Product Liability

Along with the tremendous growth of the biomedical industry is the issue of product liability litigation. There have been numerous cases where pharmaceutical and medical device manufacturers have had to remove their products from the market or file for bankruptcy due to heavy litigation and punitive damage fees. Some of the more notable examples are the experiences of the A. H Robbins Company with the Dalkon Shield intrauterine device, Merrell Dow with the drug Bendectin, and G. D. Searle & Co. with the Copper-7 intrauterine device (Price, 1987). Due to the risk associated with Class III products, it is almost impossible for medical device and drug manufacturers to buy

product liability insurance. Most often, these companies have to pay very high premiums or have self-insurance.

Most biomedical device manufacturers realize that even if a company successfully defends itself against a lawsuit, the negative publicity can be highly undesirable to the biomedical device industry. A good example was the experience of Vitek, Inc. regarding their manufacture of an implant designed to treat temporo-mandibular joint (TMJ) syndrome (Kohn, 1996). A small amount of DuPont Teflon was used in the manufacture of this implant. Vitek, Inc. was forced into bankruptcy after some of the TMJ implants failed due to the poor resistance of Teflon to continuous mechanical sheer. DuPont then withdrew its materials such as Teflon, Dacron, and Delcrin from the medical market although these materials were among the safest and most biocompatible materials available at the time. The Health Industry Manufacturers Association (1994) estimated that the withdrawal of these materials caused the shortage of 85 different medical products, affected 30 different surgical procedures, and reduced the quality of care given to an estimated 7.4 million patients.

According to Price (1987), medical device and drug manufacturers can reduce their product liability by implementing successful product safety programs. To prevent defects in design, manufacturers should choose appropriate designs for their products, document the decision-making process thoroughly, review the safety of the design chosen before actual production begins, and monitor product performance after the sale. In order to prevent defects in manufacturing, Price (1987) suggested that manufacturers use appropriate raw materials and component parts, require suppliers to assume responsibility for their products, establish rigorous quality control procedures, use appropriate methods

of packaging and shipping the product, provide sufficient instructions for the final assembly or installation of the product, and retain manufacturing documents to assist in product liability suits.

2.1.5 Social and Ethical Issues

Biomedical manufacturers also have to concern themselves with social and ethical issues when developing their products. For example, the subject of human cloning has been discussed for years and is still a much-debated issue. "Cloning" refers to the growing of a colony of genetically identical cells or organisms *in vitro* or the production of identical copies from a single entity, such as cells or genes (Cloning, 1999). Cloning is important to modern biomedical research, as it may increase the understanding of genes as well as assist in new drug and diagnostics development. However, there are groups who believe that this technology can diminish individuality and personal autonomy. It is important for biomedical companies to be aware of these different views before, during, and after the development of their products.

2.1.6 Sterilization

Medical device sterilization is treated as a special manufacturing process in the ISO 9000 series because, unlike other products, the results cannot be verified by inspecting and testing the product after the procedure. Sterilization processes must be consistently monitored, assessed, and validated before and during use. "Bioburden" is the term used describing "the population of viable microorganisms on a product and/or a package" (Satter & Sordellini, 1999). There are many factors attributing to the bioburden on the product and the packaging, such as the origin of raw materials and components,

material handling and storage factors, and the manufacturing environment in which the finished products are assembled and packaged. Therefore, a well-designed test validation should ensure that bioburden is removed from the manufactured product. The sterility assurance level (SAL) is "the probability of a viable microorganism being present on a product unit after sterilization" (Satter & Sordellini, 1999). This probability can never be reduced to zero through sterilization. However, by designing a validation program that provides a high degree of confidence for consistent sterilization, this probability can be significantly reduced. According to Satter and Sordellini (1999), microbiological performance qualification (MPQ) should be done using specified products and packaging configured similarly to that in which they will be routinely sterilized. For example, if a biomedical device manufacturer has the intention of using multiple load configurations, the densest configuration should be obtained for the MPQ. A well-designed MPQ can provide the required SAL through an economical process. It can also prevent reprocessing and delays in the release of the product, a factor important in the manufacturing of biomedical devices.

2.2 The Product Development Process

Abernathy and Utterback (1978) created a model of the product life cycle of innovation. According to this model, in the beginning phases of an industry's life, the rate of product innovation will be greater than the rate of process innovation. After experimenting with various versions of the product in the market, a main design will gradually be chosen. At this point in time, competitors will strive to manufacture similar products at lower cost and emphasis will be placed on process innovation. Therefore,

following this product life cycle model, process innovation is only of paramount importance later in the life of an industry.

During the last two decades, time-to-market has moved from obscurity to a prominent topic among product developers and manufacturers. Cost and performance are no longer the chief metrics in determining product success. First-to-market products have the advantage of commanding higher initial prices and then garnering dominant market share and customer loyalty. Numerous studies and articles (see Guveritz (1983), Fitzgerald (1987), Gold (1987), King (1987), Uttal (1987), Rosenau (1988, 1990), Dumaine (1989), Davis (1989), Gupta & Wilemon (1990), Smith (1990), Cordero (1991), Emmanuelides (1991), McDonough & Barczak (1991), Morbey (1991), Rosenthal & March (1991), Symonds (1991), and Crawford (1992)) have depicted the necessity of speed in the success of a product manufacturer and have provided suggestions on how product development cycle times can be improved.

Several techniques have been suggested to accelerate new product development, including the use of quality function deployment or QFD (Hauser & Clausing, 1988), modifying leadership styles (McDonough & Barczak, 1992), depending on external sources of technology and increasing rewards for internal research and development performance (Gold, 1987), and improving the communication between research and development and other departments such as manufacturing and marketing (Gupta et al., 1986). Table 4 provides more generic new product development acceleration approaches (Langerak et al., 1999).

Table 4: Generic New Product Development (NPD) Acceleration Approaches.

Implementation of support systems and techniques: • CAD/CAM systems • CPM and PERT • TQM • New information and communication strategies • QFD • Design for Manufacturability	**Speeding up activities/tasks:** • Speed up carrying out activities in NPD process • Link up NPD activities • Carry out NPD activities simultaneously • Elimination of slack time • Reduction of time between idea generation, screening, and development • Reduction of interdependencies between NPD activities • Emphasizing time schedules and deadlines
Reduction of parts/components in product: • Development of products of modular design • Use of existing components/parts in designing new products • When designing products, take next generation products into account • Reduction of components/parts in new products • Emphasis on incremental improvements instead of radical innovations	**Supplier involvement:** • EPA/CIM/mass customization • Supplier involvement in NPD process in early stages of NPD process • Increasing quality requirement suppliers • Contract out design, development, and production of components/parts • Involve suppliers in the production startup • Reducing the supply base • Reduction of delivery times • Implementation of JIT/KANBAN

Millson, Raj and Wilemon (1992) pinpointed five methods that companies can use to accelerate time-to-market: simplify operations, eliminate delays, eliminate steps, speed up operations, and process steps in parallel. They suggested simplifying operations by integrating tasks into meaningful groups and by simplifying documentation. Eliminating delays includes reducing marketing plans and launch delays as well as linking research and development goals to manufacturing capabilities. Eliminating steps includes reducing formal market testing, minimizing marketing department approval, minimizing the number of parts used in the manufacture of the products, and reducing the number of steps in the assembly process. To speed up operations, the use of idea-

generating groups, implementation of CAD or CAM, and installation of on-line product testing were suggested. To obtain parallel processing steps, tools such as Program Evaluation and Review Technique (PERT) and Critical Path Method (CPM) for task scheduling were suggested.

Verganti (1999) stressed the importance of planned flexibility in product development projects. Planned flexibility is "the capability to build flexibility into the development process due to decisions taken early in the project." Verganti (1999) presented 18 Italian and Swedish companies with 35 typical decisions that are usually faced in the product development process. These decisions were taken from categories such as the project plan, product concept, product and process specifications, product design choices, and process design choices. Each of the 35 decisions was reviewed and four different approaches to decision-making were identified. The approaches were summarized as either detailed, selective, comprehensive, or postponer. Companies that utilize the detailed approach are highly anticipative and spend a lot of time and effort during the early phase of a project to reduce uncertainty about downstream constraints and opportunities. Companies that use the selective approach anticipate only general and selective decisions in the early phase, giving the downstream phases the maximum degree of freedom to take advantage of unexpected opportunities. Companies that utilize the comprehensive approach combine the detailed and selective approaches by expecting as many decisions as possible in the early phase of the project. Companies that are postponers are not anticipative about downstream opportunities at all. An analysis of the performance of all 18 companies showed that none of these approaches were best for a particular company. Therefore, Verganti concluded that it was not the *choice* of the

approach to manage the early phase of a project, but the *capability* to carry on a given approach that made process development successful.

2.3 Project Management

According to Lientz and Rea (1995), a project is comprised of milestones and tasks or activities. Tasks or activities are units of work that lead to a milestone, a defined and tangible end product or goal. Project management is the process of managing, allocating, and timing resources in order to achieve a given objective in an expedient manner (Badiru, 1996). Project management encompasses planning, organizing, scheduling, and control functions. Project planning is the platform for the start, implementation, and termination of a project. This phase determines the course of actions and responsibilities required to achieve the project's goals. Project organization involves the determination of ways to integrate the functions of the personnel working in projects. The tasks involved in this phase are typically done concurrently with project planning (Badiru, 1996).

Project scheduling is time-dependent and project activities are arranged according to precedence, time, and resource constraints to accomplish the project's objectives. Schedules are made according to a standard procedure that determines the characteristics of production operations. Finally, project control ensures that suitable actions are taken to correct deviations from expected performances (Badiru, 1996).

2.3.1 Project Planning

Project planning involves the determination of guidelines such as the objectives, project structure, tasks, milestones, personnel, costs, equipment, performance, and

problem resolutions (Badiru, 1996). Badiru observed that there are three prominent levels of project planning: supralevel planning, macrolevel planning, and microlevel planning.

At the supralevel planning stage, issues are viewed in the larger context by looking at how the project fits the overall and long-range organizational goals in terms of risk exposure, management support, concurrent projects, market share, company culture, financial stability, shareholder expectation, and the effect on the diminishing company resources. The macrolevel planning level addresses the boundary of the project and its operational interfaces which include goal definition, boundary of project, personnel and resource availability, policies of the project, communication interfaces, deadlines, budget requirements, goal interactions, and conflict resolution strategies. The microlevel planning stage looks in detail at the operational plans at the task levels of the project. Issues such as scheduled time, training and tools requirement, task procedures, reporting requirements, and quality requirements are analyzed (Badiru, 1996).

In the microlevel planning phase, emphasis is placed on the comprehensiveness of details. A Work Breakdown Structure (WBS) is usually created to divide a project into greater levels of detail and measurable and controllable activities that can be easily understood in the form of a hierarchy (Dreger, 1992). The major objectives of WBS include defining the efforts made for the project, the project scope and limitations, as well as the tangible and measurable deliverables of the project. The WBS also helps to reduce the tendency to get sidetracked while working on tasks to fulfill project goals, as well as to structure the work into smaller, detailed units that make it easier to define scope and deliverables. The WBS is a hierarchical structure that is typically either an indented

listing for textual representation or a tree diagram, for graphical representation. According to Dreger (1992) and Ruskin and Estes (1995), some project managers have the tendency to skip this phase in order to save time. However, the overall costs of the project will be higher if the planning phase is improperly coordinated.

Badiru (1996) also outlined the components for a project plan. They include a brief summary of the project plan, objectives, approaches used, policies and procedures, contractual requirements, project schedule, resource requirements, performance measures, contingency plans as well as tracking, reporting, and auditing.

2.3.2 Project Scheduling

Project scheduling involves resource availability analysis of human resources, material and capital, scheduling techniques such as Critical Path Method (CPM), Program Evaluation and Review Technique (PERT), and Gantt charts, as well as tracking and reporting of the project (Kerzner, 1995). In project scheduling, a *network* is composed of events and activities. An *event* is the starting or ending point for a group of activities whereas an *activity* is the work required to proceed from one event or point in time to another. An example of a PERT network is shown in Figure 2. The circles, called nodes, represent events, and the arrows, called branches, represent activities. In the circles are numbers representing events or milestones. The number over the arrow denotes the time needed to proceed from one event to another event. Under each arrow is an activity number referencing each activity.

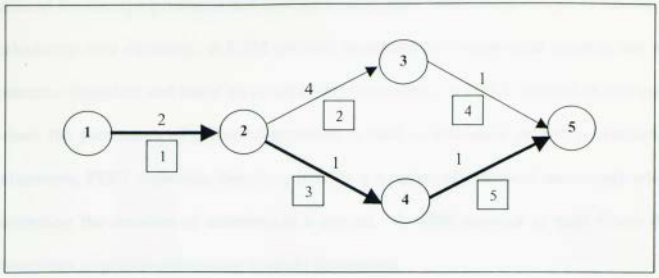

Figure 2: An Example of a PERT Network.

A sequence of activities from the starting node to the ending node is defined as a path (Pritsker et al., 1994). Events 1-2-4-5 represent the critical path of this project network because this path has no slack time. Slack time is the calculated difference between the latest allowable time on which an event can be expected to take place and the latest time at which an event can take place without extending the completion date of the project (Kerzner, 1995).

The nomenclature and principles for PERT and CPM networks are similar. According to Kerzner (1995), there are four major differences between PERT and CPM networks. A PERT network incorporates three time estimates (optimistic, most likely, and pessimistic) and derives an expected time from these estimates. A CPM network uses only one time estimate close to actual time, resulting in better estimate accuracy. A PERT network is highly dependent on probabilities, derived from a beta distribution for activity times and a normal distribution for expected activity times. Therefore, it provides for the calculation of "risk" in finishing a project. A CPM network, however, is based on one time estimate and is deterministic in nature. A PERT network is normally

utilized for managing research and development projects where there is high variability in calculating time durations. A CPM network is utilized for construction projects that are resource dependent and based on accurate time estimates. A PERT network is also used where the percentage of project completion is hard to determine except at completed milestones. PERT networks, therefore, provide a measure of statistical uncertainty when estimating the duration of activities in a project. A CPM network is used where the percentage of project completion is easily determined.

Gido (1985), Bergen (1986), and Modeler and Phillips (1970) found the following advantages of using PERT and CPM networks for project planning: provides a master plan; forces the user to think through the entire project; takes uncertainties into account; allows simulation of alternatives; provides method for reporting on progress; points out areas that are behind schedule; helps in planning resource requirements and allocations; focuses attention on the critical path; promotes awareness of project integration; helps to determine where to apply time-cost trade-offs; helps to provide overall cost control; provides the planning team with a team spirit; and helps to train new project managers.

Spera (1998) described a survey that showed a relatively high incidence of failure in meeting product development schedules for both top and average performing device manufacturers. As shown in Figure 3, the incidence rate is often in excess of 20 percent. The study followed the performance of 288 companies, 28 of which were in the medical device and diagnostic industry. In this study, "top performers" were companies in the top 20 percent of the participants based on profits from new products, product commercialization rate, and success in meeting product schedules. The schedule slip for

companies with high-complexity projects was shown to be greater than for companies with low-complexity projects.

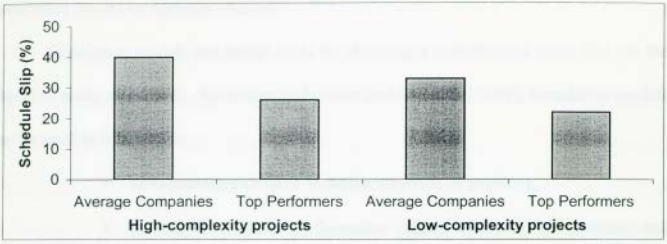

Figure 3: Incidence of Failure in Meeting Product Development Schedules for Top and Average Performing Device Manufacturers.

2.3.3 Project Control

In the project control phase, it is essential that projects be measured to find the difference between the planned performance and actual performance, and corrected to reschedule or expedite the task performance to meet the projects objectives (Badiru, 1996). These actions may also include reallocation of resources or project termination.

2.4 Simulation

With advancements in computer hardware and software technology, simulation is currently one of the most powerful modeling tools in the manufacturing area. The increasing popularity of simulation can be attributed to the introduction of computer-assisted simulation environments with speedy graphic facilities, the greater responsiveness required from current manufacturing systems due to the dynamics of the business environment, the increasing need for modeling tools for systems with stochastic

behavior and state-dependent decision mechanisms, fewer rules to follow in simulation, greater flexibility given to the modeler by simulation, and the ease of interpretation of simulation results by decision makers.

Simulation models are useful tools for defining a collection of items that are the object of study or interest. According to Pritsker and O'Reilly (1999), simulation models can be used at five levels:

- as explanatory devices to define a system or problem,
- as analysis vehicles to determine critical elements, components, and issues,
- as design assessors to synthesize and evaluate proposed solutions,
- as predictors to forecast and aid in planning future developments, and
- as part of a system to provide on-line monitoring, status projections and decision support.

The scope, boundaries, and contents of a simulation model are dependent on particular problems the model is designed to solve. According to Law and Kelton (1991), simulation models also allow the assessment of potential performance before a newly designed system is operable, the comparison of various operating schemes of a present system without altering the ongoing performance of the system, and time compression or expansion of the system's operation.

Pritsker et al. (1994) proposed the following iterative steps in the modeling and simulation process:

- formulate the problem,
- specify the model,

- build the model,
- simulate the model,
- use the model, and
- support decision making.

To build a strong simulation model, it is essential to first formulate the problem by comprehending the problem, identifying the goals, specifying performance measures, setting model objectives, and defining the system to be modeled. Second, the model is specified by identifying the assumptions, data requirements, components, and the interaction of those components. Third, the model is built by drawing out the simulation model, collecting required data, and by defining the experimental controls. The model is then simulated. In this stage, the model is run, verified, and validated. After running the model an appropriate number of times, the interpretation and presentation of the outputs is performed. Finally, the results are used to support decision-making (Pritsker et al., 1994).

2.4.1 Simulation as a Tool for Project Planning, Scheduling and Control

Activity planning, scheduling, and control are fundamental in the managing of manufacturing systems. Although there are many advantages of using PERT and CPM networks for project planning, Wiest and Levy (1977) suggested that PERT networks have the problem of providing overoptimistic results in many applications. Gido (1985) and Bergen (1986) also presented the following disadvantages of PERT and CPM networks:

- the methods will not make decisions,
- analyzing the networks can be expensive,

- may lend credence to poor data,
- may give a false sense of security,
- networks can cross organizational bounds,
- do not display work loads,
- the level of detail may become confusing, and
- major revisions are difficult to incorporate into existing networks.

Pritsker et al. (1994) also stated that PERT networks have the following constraints:

- the number of activity completions required to release a node is equal to the number of branches ending at a node,
- all branching is done on a deterministic basis,
- no cycles (feedback) are allowed in the network, and
- projects are always completed successfully, as the concept of failure is nonexistent.

Although PERT and CPM networks provide good communication vehicles to describe large projects in network form, Pritsker et al. (1994) suggested the use of simulation to counter these network constraints. PERT and CPM networks also have many limitations in terms of addressing issues of uncertainty. Mongalo & Lee (1990) proposed that uncertainties imposed by random variables be countered by using a simulation technique called the Monte Carlo Sampling Technique (MCST). This technique involves the random selection of activity times from an appropriate frequency distribution. The critical path and the time needed to complete the project are determined using these results. The degree of accuracy of the MCST model is dependent on the

number of times the procedure is repeated. The output summary of the MCST provides values for the mean and variance of the project duration, produces the criticality index, which is the probability of an activity being on the critical path, and the project risk, which is the probability of the project being delayed after it is supposed to be completed.

Mongalo and Lee (1990) attempted to determine the network characteristics that make the use of simulation preferable to the use of a PERT network. The results of their study revealed that on many occasions, the project durations produced by PERT and MCST were statistically different. The underestimations of project completion times provided by PERT were mainly due to parallelism, size, and their interaction. The varying project completion times given by PERT and MCST were found to be due to the types of distributions used. Normally-distributed activities provided the shortest project duration estimates, whereas values taken from uniformly-distributed frequencies provided the largest project duration estimates. The beta and triangular distributions yielded statistically similar conclusions. Mongalo and Lee (1990) noted that, in many cases, the PERT method concluded that the project would be completed as scheduled, while the MCST method projected that there were high risks that the project would not be completed on time. They also observed that the MCST method for estimating project duration time was time-consuming.

Badiru (1991a) developed a computer simulation program named STARC to aid in project planning. STARC was developed to simulate project networks and perform "what-if" analysis of projects involving probabilistic activity times and resource constraints. STARC is a menu-driven program compiled in the BASIC programming language for IBM-compatible computers. In project scheduling, STARC makes the

following assumptions: resource availability is in whole units; no partial assignments of resources; splitting of activities and activity preemption are not allowed; total resource units required must be available before an activity can start; and all predecessors must be finished before an activity can start.

In his approach to simulation modeling, Badiru (1991b) first conducted PERT activity time modeling. Second, the project network was simulated using STARC. Third, managerial decisions were made based on the simulation output. The last step in the process consisted of running a statistical analysis of the simulation output using STATGRAPHICS software. The study concluded that simulation is an effective tool to enhance planning and control methods in project management, as the methods and what-if analyses that are provided with the simulation are very beneficial to project analysts who must take uncertainties in project scheduling into consideration.

The Graphical Evaluation and Review Technique (GERT) was developed to analyze networks with stochastic activities and decision nodes (Pritsker & Happ, 1966). GERT is an extension of PERT and CPM networks as PERT and CPM can be classified as a special class of GERT networks. The Venture Evaluation and Review Technique (VERT-3) was designed as another network modeling technique and computerized analysis system to assist in decision-making processes. This technique takes into consideration the time, cost, and performance at each node and branch, and generates critical paths for time, money and performance measures (Lee et al., 1982). These techniques provide the basis for simulation modeling networks such as SLAM II, Visual SLAM, and SIMAN that exist today.

2.4.2 Computer Simulation Languages

Computer simulation began with programming languages such as C (Crookes, 1989), C++ (Joines et al., 1992), Pascal (Pidd, 1989), Fortran, and Basic (Pidd, 1988). However, these languages require extensive knowledge of coding and the development of simulation models was very slow. Process-oriented simulation languages such as SLAM II (Pritsker, 1986), SIMAN (Pegden et al., 1986), and SIMSCRIPT (Greene, 1997) have been successful in decreasing the programming burden on the simulation modeler. These languages provide subroutines for time advancement, entity maintenance, and statistics collection.

When given a model description, SLAM II is a language that converts the description into a form that can be recognized by the computing system (Pritsker & O'Reilly, 1999). The user analyzes the outputs and makes appropriate changes to the model to find the optimal solution to the defined problem. The functions in SLAM II are accessible through pull-down menus and dialog boxes chosen from the SLAM II Executive Window. AweSim 3.0 is a software that provides graphical implementation of the SLAM II language as well as a simulation problem-solving environment for Visual SLAM (Pritsker & O'Reilly, 1999).

CHAPTER 3

PROBLEM STATEMENT

The main objective of this thesis was to develop the Biomedical Operations Project Planning (BOPP) methodology and to explore the application of simulation (in particular, SLAM II) as a tool for project planning in biomedical device product and process development. An extensive literature search was performed to identify and detail the challenging areas in the manufacture of biomedical devices. These include biomedical device manufacturing technologies, biomedical device integration with the human body, government regulations on biomedical devices, biomedical product liability, social and ethical issues, and sterilization (Grant, 1999). The literature review also showed that strategic planning and planned flexibility are essential to ensure the growth of a company.

The purpose of this research was to show that the use of computer simulation can help biomanufacturing companies in incorporating planned flexibility and strategic planning in product and process development, while addressing the challenges in the field of biomanufacturing. This objective was satisfied through the development of the BOPP methodology.

The primary objectives of project scheduling are to make a product in the least amount of time, with the least cost and risk (Kerzner, 1995). In the biomanufacturing industry, well-planned process development can ensure rapid time-to-market, fast production ramp-up, increased customer acceptance of new products, and a more solid proprietary position for biomanufacturers (Pisano, 1997). Although much research has

been done depicting the necessity of reducing time-to-market, none have focused on the booming biomedical device industry, where speed in product and process development is of paramount importance. Biomedical device technology changes so quickly that these products need to be released into the marketplace as quickly as possible to recoup the investment made in them.

It is also particularly important for biomanufacturers to be able to estimate the risks involved in the decision-making process due to the time constraints and high costs associated with the biomedical device industry. In this application, risk is measured as the probability that a project plan will exceed the due dates or fail.

Although many suggestions have been made on how to improve product development cycle times and how to increase speed in manufacturing, no research has been done to investigate the use of simulation as a project management tool to accelerate biomedical device product and process development. Furthermore, no previous research was found that considered the many issues that make biomanufacturing unique in the manufacturing industry or concentrated on the risks involved in decision-making in biomanufacturing.

Therefore, this thesis satisfied two of the three objectives of project planning by investigating the features in SLAM II that make it possible and advantageous for this language to be used in determining project durations and risks. Due to the difficulty in accessing cost information from biomedical device companies, this research did not attempt to include costs as a factor in project planning. This research also provided necessary data collection and general biomedical device simulation model templates, thereby providing project planners with the option of either developing simulation

models using the BOPP methodology or modifying the templates to suit the needs of unique biomedical devices.

The BOPP methodology developed in this thesis addressed the following unique requirements in the development and manufacture of biomedical products: product development and process development failure and reengineering of those activities; government regulations and the approval process, along with its impact on product and process development; and multiple subprocess failures with time variant probabilities.

Finally, a model of the product and process development of an insulin pump is provided as an example application of the BOPP methodology. The development of the BOPP methodology for product and process development in the biomedical device industry through the use of computer simulation is addressed in the next chapter.

CHAPTER 4

METHODOLOGY

This chapter presents BOPP, a methodology that was created during this research for using computer simulation as a tool for project planning in biomedical device product and process development. An assumption was made during the development of this methodology that the project planner has intermediate understanding and knowledge of the SLAM II language and is familiar with the AweSim 3.0 software. Details regarding this language can be found elsewhere (Pritsker et al., 1994; Pritsker and O'Reilly, 1999; Pritsker, 1986).

A summary of the BOPP methodology is provided in Figure 4 in the form of a flowchart. The first step of the BOPP methodology is to collect the necessary data to create the project plan model. The second step is to determine the Task Groups of the biomedical device product and process development. A Task Group is a set of tasks focusing on a certain area in the product or process development such as Research and Development, Manufacturing, or Regulatory. The third step is to determine the Primary Tasks within each Task Group. Primary Tasks are the specific main tasks that must be performed within each Task Group. The fourth step is to determine Secondary Tasks. Secondary Tasks are tasks within Primary Tasks that represent more detail to facilitate project planning. The fifth step of the BOPP methodology is to estimate all task durations. Each task is provided a triangular distribution of an estimated longest (MAX), most frequent (MODE), and shortest (MIN) time.

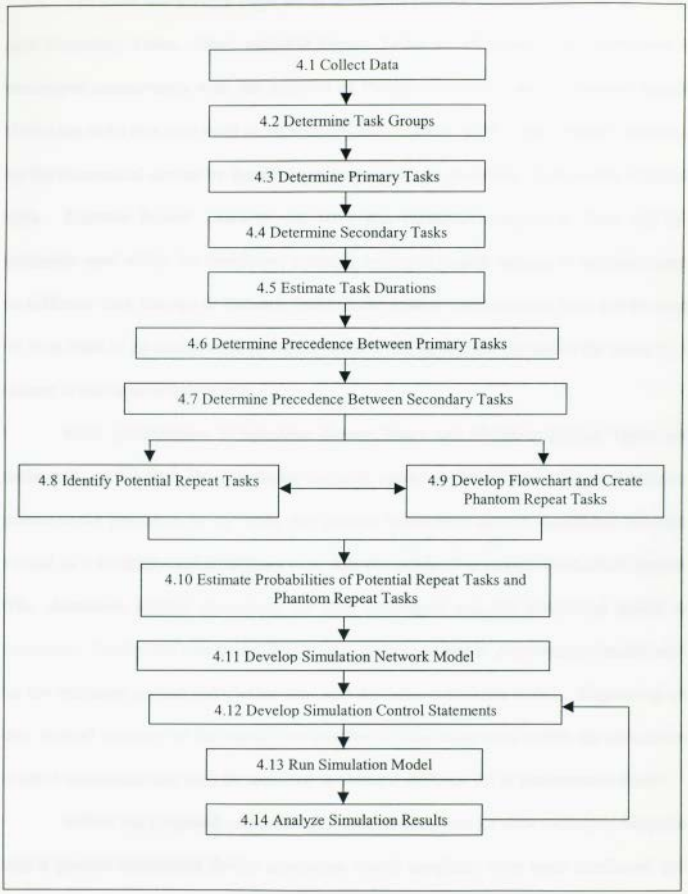

Figure 4: Biomedical Operations Project Planning (BOPP) Methodology.

The sixth and seventh steps are to determine precedences between Primary Tasks and Secondary Tasks. Next, potential Repeat Tasks are identified, and a flowchart is developed concurrently with the creation of Phantom Repeat Tasks. Potential Repeat Tasks are tasks that may need to be repeated either due to performance failure, rejection of the biomedical device by the FDA, or merely for the necessity of obtaining repeated data. Phantom Repeat Tasks do not have any durations assigned to them and are primarily used within the simulation model to represent logical looping of activities back to different Task Groups or Primary Tasks in the model. For example, they can be used to loop back to an earlier time to repeat tasks in the simulation model in the event of a failure in one area of the project.

Next, probabilities of potential Repeat Tasks and Phantom Repeat Tasks are estimated. After that, the simulation network model is developed using the different subnetworks provided, or by using the general biomedical device simulation network model as a template and modifying it to suit the needs of a certain biomedical device. The simulation control statements are then developed and the simulation model is executed. Finally, the results are analyzed to determine initial performance results such as the estimated project completion time and the risks associated with it. Depending on the desired accuracy of the results, the number of simulation runs within the simulation control statements may then be modified to obtain a different set of performance results.

Within the proposed methodology, general templates (a data collection template and a general biomedical device simulation model template) have been developed and provided for the project planner to facilitate the use of this methodology in the project planning process. The data collection template is in table form, as shown in Table 5.

This template requires information such as Task Groups (Column 4.2), Primary Tasks (Column 4.3), Secondary Tasks (Column 4.4), estimated durations of tasks (Column 4.5), Primary Task Precedences (Column 4.6), and Secondary Task Precedences (Column 4.7). The general biomedical device simulation model template is developed using the data collection template and is presented later, in Section 4.11.8.

The following discussion provides details on each of the steps in the BOPP methodology.

4.1 Collect Data

The first step in project planning for biomedical device product and process development is to collect the necessary data to create the project plan model. In order to do so, it is necessary to define the function of the biomedical device as well as to determine the components or parts of the biomedical device. In the development of BOPP, it is assumed that the physical design of the biomedical device has been completed. Data collection can be achieved through two methods: extensive literature research on biomedical device manufacturing and consultation with experts in the biomanufacturing field. For example, in order to determine the components of a biomedical device, documents such as the Bill Of Materials (BOM) may be used. Although most start-up manufacturing firms will not have documents like these in place, it is possible to obtain BOM samples related to a particular biomedical device from an external consulting firm, or even from another manufacturing company. This information will be helpful in determining the components of the biomedical device, the raw materials required to produce the biomedical device, and how it should be manufactured.

Table 5: General Biomedical Device Project Planning Task Groups and Precedences Summary.

Task Group (4.2)	Primary Task (4.3)	Secondary Task (4.4)	Duration (4.5)	Primary Task Precedence (4.6)	Secondary Task Precedence (4.7)
RD	Determine Biomedical Device Components (Components)	None (RD_1)	TRIAG (X,Y,Z)		
	Identify Raw Materials (Raw)	Research and Specify Raw Materials for Biomedical Device (RD_2)	TRIAG (X,Y,Z)	Components	
		Test for Suitability of Raw Materials for Biomedical Device (RD_3)	TRIAG (X,Y,Z)		RD_2
	Determine Production Assembly Process (Prod)	None (RD_4)	TRIAG (X,Y,Z)	Raw	
	Determine and Test Sterilization Method (Sterilization)	Determine Sterilization Method (RD_5)	TRIAG (X,Y,Z)	Prod	
		Analyze Effects of Sterilization (RD_6)	TRIAG (X,Y,Z)		RD_5
		Analyze Particulate Contaminants (RD_7)	TRIAG (X,Y,Z)		RD_6
	Determine Biocompatibility (Biocompatibility)	Run Tests To Investigate Biocompatibility (RD_8)	TRIAG (X,Y,Z)	Sterilization	
		Perform Failure-Mode-Effect Analysis (RD_9)	TRIAG (X,Y,Z)		RD_8
	Identify Storage Criteria (Storage)	None (RD_10)	TRIAG (X,Y,Z)	Sterilization	
	Determine Packaging Material (Packaging)	Identify Packaging Material (RD_11)	TRIAG (X,Y,Z)	Sterilization	
		Evaluate Packaging Material (RD_12)	TRIAG (X,Y,Z)		RD_11

Table 5: General Biomedical Device Project Planning Task Groups and Precedences Summary (Cont.).

Task Group (4.2)	Primary Task (4.3)	Secondary Task (4.4)	Duration (4.5)	Primary Task Precedence (4.6)	Secondary Task Precedence (4.7)
MFG	Construct Preliminary GMP Manufacturing Facility (GMP)	None (MFG_1)	TRIAG (X,Y,Z)	Prod	
	Identify and Qualify Alternate Vendors (Vendor)	None (MFG_2)	TRIAG (X,Y,Z)	GMP	
	Install New Equipment (Equipment)	None (MFG_3)	TRIAG (X,Y,Z)	Vendor	
	Establish Formal Production Process (ProdProcess)	Establish Formal Production Process (MFG_4)	TRIAG (X,Y,Z)	Biocompatibility, Storage, Packaging, Equipment	
		Determine Batch Size and Frequency of Manufacturing (MFG_5)	TRIAG (X,Y,Z)		MFG_4
		Discuss with Research Team and Confirm Each Step of Production Process (MFG_6)	TRIAG (X,Y,Z)		MFG_5
		Propose New Techniques and Equipment for Scale-up Manufacturing (MFG_7)	TRIAG (X,Y,Z)		MFG_6
	Manufacture, Assemble, and Test Biomedical Device Components (Manufacture)	Manufacture Biomedical Device Components (MFG_8)	TRIAG (X,Y,Z)	ProdProcess	
		Assemble Biomedical Device Components (MFG_9)	TRIAG (X,Y,Z)		MFG_8
		Test Biomedical Device Components (MFG_10)	TRIAG (X,Y,Z)		MFG_9
		Assemble Final Biomedical Device (MFG_11)	TRIAG (X,Y,Z)		MFG_10

Table 5: General Biomedical Device Project Planning Task Groups and Precedences Summary (Cont.).

Task Group (4.2)	Primary Task (4.3)	Secondary Task (4.4)	Duration (4.5)	Primary Task Precedence (4.6)	Secondary Task Precedence (4.7)
MFG (Cont.)		Test Final Biomedical Device (MFG_12)	TRIAG (X,Y,Z)		MFG_11
		Validate Biomedical Device Processing Events (MFG_13)	TRIAG (X,Y,Z)		MFG_12
	Ensure Environmental Controls Follow Regulations (Environment)	None (MFG_14)	TRIAG (X,Y,Z)	Manufacture	
	Perform Clinical Testing (Clinical)	None (MFG_15)	TRIAG (X,Y,Z)	IDE	
REG	File for Investigational Approval from IRB (IA)	None (REG_1)	TRIAG (X,Y,Z)	Environment	
		WAIT	TRIAG (X,Y,Z)		
	Submit Investigational Device Exemption to FDA (IDE)	None (REG_2)	TRIAG (X,Y,Z)	IA	
		WAIT	TRIAG (X,Y,Z)		
	Submit for Premarket Notification (PMN)	None (REG_3)	TRIAG (X,Y,Z)	Clinical	
		WAIT	TRIAG (X,Y,Z)		
	Prepare Biomedical Device For Market	None (PREPMARKET)	TRIAG (X,Y,Z)	PMN	
BIOMEDICAL DEVICE READY FOR MARKET					

It is important to emphasize that obtaining detailed BOM information may be difficult due to proprietary interests. However, for the purpose of creating a project plan model for biomedical device product development and manufacturing, only information regarding the basic top-level components of the medical device is needed, and this information can usually be acquired with minimal difficulties.

Besides defining the components of the biomedical device, it is also important to gather information regarding necessary tasks for the product development and manufacturing of the biomedical device. Tasks are the most basic building blocks of project planning. They define the work to be done to meet the goals of a project. A majority of the information needed to create the methodology for general biomedical device product and process development was obtained from the work of DeSain (1993) as well as through interviews and correspondence with experts on the subject of biomedical device process development and manufacturing (J. Livingston, personal communication, June 19, 2000).

These research and consultation activities should not only place emphasis on the actual manufacturing of medical devices, but also on the FDA regulations on these devices, as well as Good Manufacturing Practices (GMP). The information collected in this step will be utilized to determine the essential Task Groups as well as Primary and Secondary Tasks in manufacturing a biomedical device.

4.2 Determine Task Groups

The second step is to determine the necessary Task Groups for product development and manufacturing of the biomedical device. A Task Group is a set of tasks focused on a particular phase of product or process development. Most often, there are

three main phases or Task Groups in biomedical device product and process development. They are Research and Development (RD), Manufacturing (MFG), and Regulatory (REG). These Task Groups are shown in Column 4.2 in Table 5.

The RD Task Group may also be referred to as the Product Development Task Group. Biomedical device research describes and classifies substances or processes deemed useful for therapeutic or diagnostic application (DeSain, 1993). This objective is fulfilled by exploring research or design choices in order to obtain a rationale for the product design. Biomedical device product development extends the basic research ideas to build a prototype or design of the device. The MFG Task Group is related to the actual manufacturing of the biomedical device, and is also known as the Process Development Task Group. The REG Task Group is related to regulatory issues in the manufacturing of biomedical devices.

4.3 Determine Primary Tasks

The next step in the project planning of biomedical device product development and manufacturing is to determine all the Primary Tasks within each Task Group. Primary Tasks are essential tasks to be completed within each Task Group. Primary Tasks within RD include assessing and choosing raw materials, determining manufacturing options, and evaluating the product performance or reliability. According to DeSain (1993), it is also in the research and development stage of a medical device that the required raw materials, quality requirements, product sensitivities, assembly requirements and methods, and product evaluation methodology is determined.

The Primary Tasks within the MFG Task Group include the construction of a preliminary GMP manufacturing facility, qualification of vendors, installation of new

equipment, confirmation on the final production process, as well as the manufacturing, assembly, and testing of each component of the biomedical device while ensuring safe environmental controls.

The REG Task Group includes Primary Tasks such as obtaining the approval from an Institutional Review Board (IRB), submission for Investigational Device Exemption (IDE) to the FDA, and submission for Premarket Notification (PMN), also known as 510K, or submission for Premarket Approval (PMA) (FDA, 2000a). Approval from the IRB is necessary as this committee must confirm that they will supervise the testing of the biomedical device, will provide approved, informed consent forms to the patients, and will ensure that proper records and reports are filed. After obtaining the approval from the IRB, the IDE is usually filed. The approval of this application provides permission for the manufacturer to use the product within the state commerce for investigational purposes only. It also allows the manufacturer to perform clinical testing without strict adherence to the Food, Drug and Cosmetic (FD&C) Act. Then, depending on the classification of the medical device, a PMN or PMA is filed. A PMN is a document submitted to the FDA when a medical device is to be commercially introduced, but does not require a PMA (FDA, 1998). These devices are typically Class I devices, and some Class II and Class III devices that are already in the market and have been determined to be safe and effective by the FDA. A device requiring PMA approval is one which:

- was not on the market before May 28, 1976, and is not substantially equivalent to a device on the market before May 28, 1976, or to a device first marketed on or

after that date, which has been classified into Class I (General Controls) or Class II (Special Controls), or

- is required by a regulation issued under 515(b) of the FD&C Act to have an approved premarket approval application (PMA) or a declared completed product development protocol (PDP), or
- was regulated by the Food and Drug Administration (FDA) as a new drug or an antibiotic drug before May 28, 1976, and therefore is governed by 520(l) of the FD&C Act (transitional devices) (FDA, 2000b).

Unlike the PMN, a PMA application is dependent on sufficient valid scientific evidence that provides assurance that the device is safe and effective for its intended use or users (FDA, 2001). Column 4.3 in Table 5 identifies common Primary Tasks for biomedical device product and process development. Each of the tasks is given a unique label so that it will be easily identifiable in the future. For example, the Primary Task, "Determine Biomedical Device Components" is given the label "Components."

4.4 Determine Secondary Tasks

After specification of Primary Tasks, Secondary Tasks are determined, if any. Secondary Tasks are Primary tasks that are broken down so that they are easier to manage for project planning purposes.

Column 4.4 in Table 5 identifies Secondary Tasks within the Primary Tasks for biomedical device product and process development. Like Primary Tasks, the Secondary Tasks are also given unique labels for ease of future identification. All the Secondary Tasks within the RD Task Group are given labels that started with "RD", followed by an

underscore and a number. For example, the Secondary Task, "Research and Specify Raw Materials for Solenoid Motor" is given the label, "RD_2." Similarly, all the Secondary Tasks within the MFG Task Group are provided labels that start with "MFG", followed by an underscore and a number. All of the Secondary Tasks within the REG Task Group are provided labels that start with "REG", followed by an underscore and a number. If a Primary Task is not broken down into Secondary Tasks, a label with the same format is also provided within this column.

Tasks that fall under the "REG" category usually have WAIT times. WAIT time is used when an application for FDA approval is submitted and the company has to wait for a response before proceeding to the next task. Therefore, each task within this category is allowed WAIT time within the Secondary Task column.

The final task is usually to "Prepare Biomedical Device for Market", and is labeled "PREPMARKET."

4.5 Estimate Duration of Tasks

All durations of Secondary Tasks as well as Primary Tasks that are not comprised of any Secondary Tasks are then specified. The durations of Primary Tasks that are comprised of Secondary Tasks do not need to be specified because the sum of the durations of all Secondary Tasks within a Primary Task is the duration of that Primary Task. For simulation modeling purposes, the required data are estimates of the longest (MAX or "X"), most frequent (MODE or "Y"), and shortest (MIN or "Z") possible duration for each of these tasks. A triangular distribution that includes these durations was chosen because the project planner may not actually know the distribution of the project durations but should find it relatively easy to provide the longest, most frequent,

and shortest durations of the tasks. Hence, the triangular distribution will provide a good approximation. Estimated durations are obtained from sources such as historical data, estimates from personnel who will perform the required tasks, and expert opinions from project managers, professionals or industry organizations that have experience on similar projects (Chatfield & Johnson, 2000). Since these durations vary with different projects and are often manipulated, it is not possible to generalize a duration for each task. Therefore, it is left up to the project planner to estimate the task durations for Column 4.5 in Table 5.

4.6 Determine Precedences between Primary Tasks

It is also necessary to determine precedences between Primary Tasks. Precedences occur when the ending event for a task must happen before starting another task. It is possible that several Primary Tasks must end before the start of another Primary Task. Column 4.6 in Table 5 shows precedences for the biomedical device product and process development Primary Tasks determined in Section 4.3. These Primary Task links were determined by linking and confirming information in DeSain's handbook through correspondence with experts in biomedical device product and process development (J. Livingston, personal communication, June 19, 2000).

4.7 Determine Precedences between Secondary Tasks

The precedences between Secondary Tasks are similarly determined, by taking into consideration that the ending event for more than one Secondary Task may occur before the start of another Secondary Task. Column 4.7 in Table 5 shows precedences

for the biomedical device product and process development Secondary Tasks determined in Section 4.4.

4.8 Identify Potential Repeat Tasks

Due to the strict regulations in biomedical device manufacturing, as well as the complexity of the biomedical device itself, there are many instances where the need arises for tasks to be repeated, either due to performance failure, rejection of the biomedical device by the FDA, or merely due to the necessity of obtaining repeated data. These tasks are called Repeat Tasks. The identification of potential Repeat Tasks is performed while developing the flowchart in Section 4.9. One example of a potential Repeat Task is the Secondary Task, "Determine Sterilization Method (RD_5)." This task may be repeated if the tests performed in Secondary Tasks, "Analyze Effects of Sterilization (RD_6)" or "Analyze Particulate Contaminants (RD_7)" fail to pass a chosen sterilization method. Likewise, after Secondary Task, "Evaluate Packaging Material (RD_12)" is performed, it is possible that the chosen packaging material is deemed unsuitable. Therefore, there is a possibility of repeating the Secondary Task, "Identify Packaging Material (RD_11)" to recommend another type of packaging material to be tested.

4.9 Develop Flowchart and Create Phantom Repeat Tasks

Using the information gathered from Sections 4.1 to 4.8, a flowchart is developed to provide a pictorial flow of a general biomedical product and process development project. If the project planner chooses to use the information in Table 5, he or she can

also utilize this flowchart and if necessary, modify it according to his or her unique needs.

The flowchart in Figure 5 shows that the general biomedical device product and process development is comprised of the three major Task Groups: RD, MFG, and REG. The RD phase involves the research and development of raw materials and their preparation for manufacturing. The MFG phase is the actual manufacturing of the biomedical device. The REG phase involves the handling of documents for the regulatory approval processes.

In the BOPP methodology, it is assumed that the RD phase begins after confirmation of a biomedical device design. First, the components of the biomedical device are determined (RD_1). Once this has been done, the raw materials for each of the components is researched and documented (RD_2). The raw materials are then all tested to determine whether they are suitable for the biomedical device (RD_3). Raw material tests include infrared or nuclear magnetic resonance, density, hardness, porosity, elasticity, radiopacity, morphology, gas or moisture permeation, wetting characteristics of surface, thermal properties, stress-strain relationships, physico-chemical tests of extractables or leachables, particulate contaminants and electromagnetic radiation effects (DeSain, 1993). The cost of the planned raw materials is also taken into consideration. This process is iterated until suitable raw material for each component is found. Once the raw materials are confirmed, the production assembly process is determined (RD_4). The determination of the production assembly process is done while placing the utmost importance on quality issues. At this point, the MFG

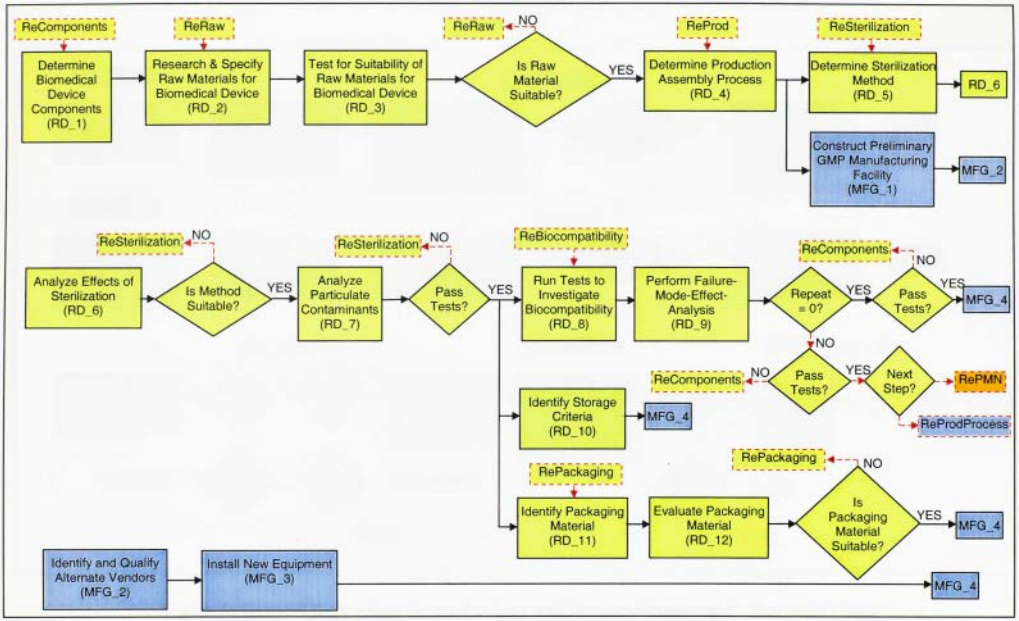

Figure 5: General Biomedical Device Product and Process Development Flowchart.

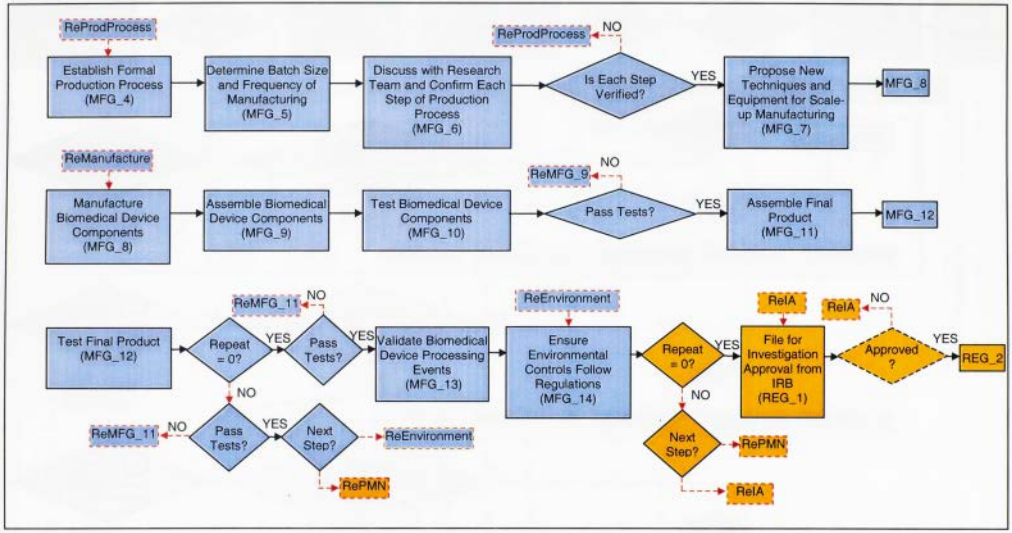

Figure 5: General Biomedical Device Product and Process Development Flowchart (Cont.).

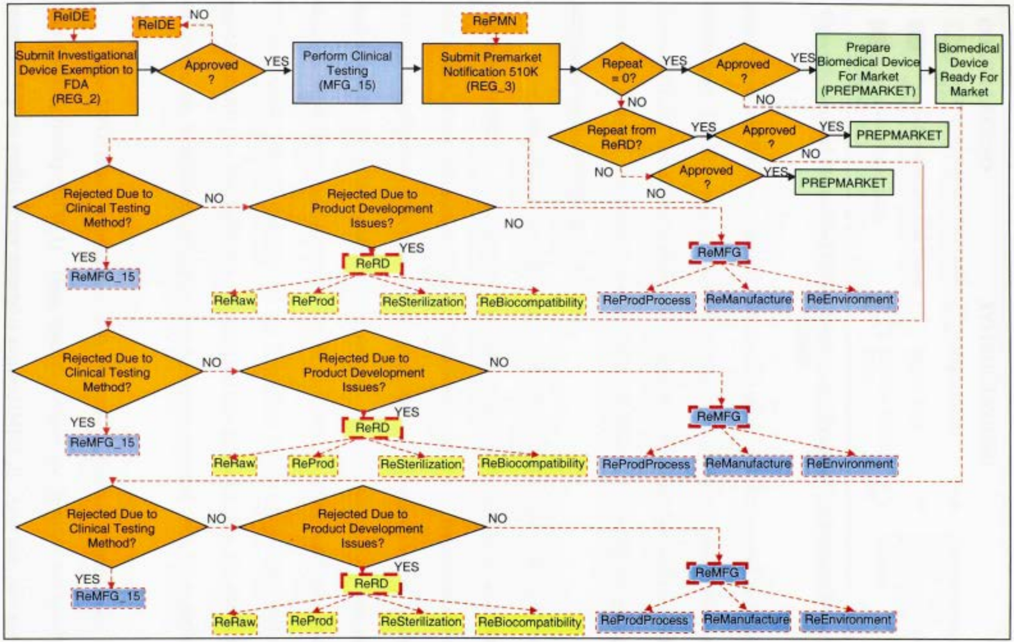

Figure 5: General Biomedical Device Product and Process Development Flowchart (Cont.).

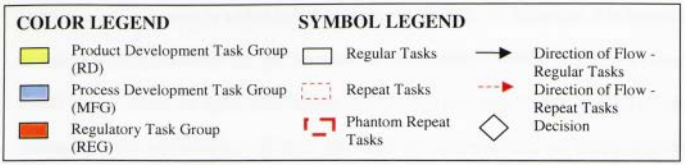

Figure 5: General Biomedical Device Product and Process Development Flowchart (Cont.).

phase begins and flows concurrently with the RD phase in order to speed up design-to-market time. The RD phase is continued with the determination of sterilization method options (RD_5). The effects of different sterilization methods are then analyzed (RD_6), and one is selected. As shown in the flowchart, the process of finding the appropriate sterilization methods is also an iterative one.

After a sterilization method is determined, the method is analyzed for particulate contaminants (RD_7). If the level of particulate contaminants exceeds the level allowed by the FDA, a new sterilization method is determined. Otherwise, biocompatibility tests (RD_8), identification of storage criteria (RD_10), and identification of packaging materials (RD_11) are then performed concurrently. After biocompatibility tests are run, failure-mode-effect analysis is performed (RD_9). If discouraging results are produced by this analysis, the requirements for the biomedical device components need to be reanalyzed (RD_1). The packaging materials are also evaluated (RD_12), and if found unsuitable, the identification of appropriate packaging materials (RD_11) is performed again.

The MFG phase is initialized with the construction of a preliminary GMP manufacturing facility (MFG_1). Then, alternate vendors are identified and qualified to assure the highest quality of raw material is acquired (MFG_2). After that, new and more

sophisticated equipment is added into this facility (MFG_3). At this point, it is important to note that the precedence for the next task of establishing a formal production process (MFG_4) are all of the tasks involved in determining biocompatibility, storage criteria, packaging, and equipment. This is followed by determination of batch size and frequency of manufacturing (MFG_5). Then, each step of the production process is discussed with the research team to verify the process (MFG_6). If a problem is found within the proposed production process, an effort is made to revise the new production process until one can be finalized and implemented. Otherwise, new techniques and equipment for scale-up manufacturing are proposed (MFG_7). All biomedical device components are then manufactured in batches (MFG_8). Next, the biomedical device components are assembled (MFG_9) and tested (MFG_10). This process is iterated until high quality biomedical device components are manufactured. Then, all of the components are assembled to form the final product (MFG_11) and tested (MFG_12). Once the final product passes all tests, the biomedical device processing events are validated to ensure consistent processing (MFG_13). Then environmental controls are checked to ensure that they follow federal and state government regulations (MFG_14).

At this point, the FDA REG process is begun. An Investigation Approval (IA) is filed and submitted to an Institutional Review Board or IRB (REG_1). This document is revised until it is approved by the IRB. Then, following approval, an Investigational Device Exemption (IDE) is submitted to the FDA (REG_2). This document is also revised until approved by the FDA. Clinical testing is then performed (MFG_15) and a Premarket Notification (PMN) is submitted to the FDA (REG_3). If not approved by the FDA, the process could be repeated at the Product Development phase (ReRD), Process

Development phase (ReMFG), or at clinical testing (ReMFG_15), as depicted in the flowchart of Figure 5. For example, if problems are determined by the FDA to be in the product development stage (ReRD), it may be possible that the problems are related to the raw materials (ReRaw), production assembly process (ReProd), sterilization method (ReSterilization), or biocompatibility (ReBiocompatibility). If problems are determined by the FDA to be in the process development stage (ReMFG), it is possible that the problems are related to the production process (ReProdProcess), actual manufacturing (ReManufacture), or environmental controls (ReEnvironment). After correcting the problems, the PMN is resubmitted to the FDA. Upon final approval by the FDA, the biomedical device is ready to be manufactured in full-scale for mass market (PREPMARKET).

All tasks that have labels that begin with "Re" represent Phantom Repeat Tasks and Repeat Tasks as shown in Figure 6. Repeat Tasks are activities that may have to be repeated due to failure. These tasks do not have durations but probabilities assigned to them, representing the probabilities of activity failure. Phantom Repeat Tasks are tasks that are used as logical loops back to earlier in the simulation model to different Task Groups and Primary Tasks when the application is rejected by the FDA. Therefore, like Repeat Tasks, Phantom Repeat Tasks also do not have durations but probabilities assigned to them, to represent the probabilities of these logical loops occuring. The FDA may reject the application for Premarket Notification (REG_3) due to various reasons, and therefore, action needs to be taken to correct these problems before resubmitting the application to the FDA. In order to model these, Phantom Repeat Tasks are used. For

example, it was determined that the FDA may reject the PMN due to problems either in the RD or MFG phases. These are represented by the labels, "ReRD" and "ReMFG."

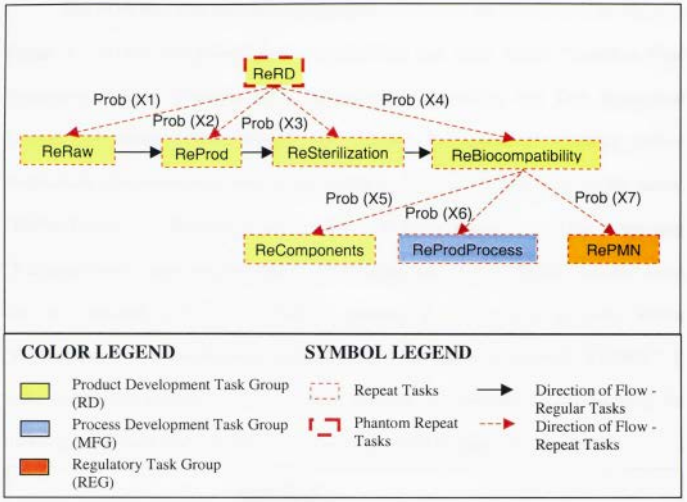

Figure 6: Phantom Repeat Tasks Flow at Product Development (RD).

Within the RD phase, it is possible that the problems lie either within the Primary Tasks of "Identify Raw Materials (Raw)", "Determine Production Assembly Process (Prod)", "Determine Sterilization Method (Sterilization)", or "Determine Biocompatibility (Biocompatibility)" (Figure 6). These are represented by the labels, "ReRaw", "ReProd", "ReSterilization", and "ReBiocompatibility". If a task within "ReProd" is repeated, tasks within "ReSterilization" and "ReBiocompatibility" are also repeated. After tasks within "ReBiocompatibility" have been completed, there are probabilities that tasks within "ReComponents" or "ReProdProcess" need to be repeated.

Otherwise, an application for PMN is submitted again to the FDA, represented by "RePMN".

The FDA may also determine that the problems lie in the MFG phase, as shown in Figure 7. Within this phase, there is probability that tasks within "Establish Final Production Process (ProdProcess)", "Manufacture, Assemble, and Test Biomedical Device Components (Manufacture)", or "Ensure Environmental Controls Follow Regulations (Environment)" need to be repeated. These are represented by the labels, "ReProdProcess", "ReManufacture", and "ReEnvironment". After repeating "ReManufacture", there are possibilities of repeating tasks within "ReManufacture" again due to repeated performance failure, proceeding and repeating tasks within "ReEnvironment" or resubmitting application for PMN approval, through "RePMN." If tasks within ReEnvironment are repeated, there is a possibility of resubmitting for Investigational Approval, "ReIA" or resubmitting for PMN approval, "RePMN".

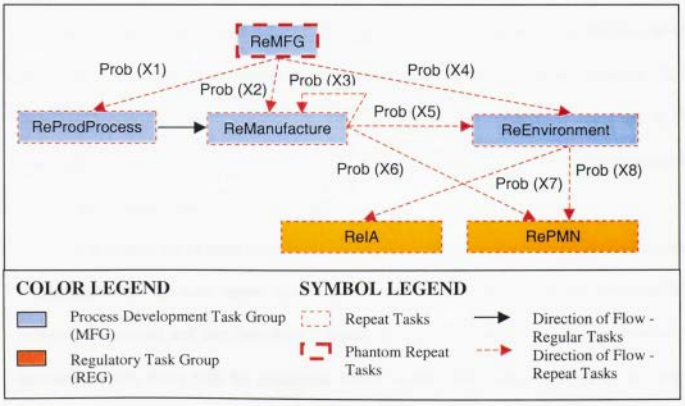

Figure 7: Phantom Repeat Tasks Flow at Process Development (MFG).

Once Primary, Secondary, Repeat, and Phantom Repeat Tasks within the RD and MFG phases have been identified, it is necessary to ensure consistency of the flowchart with the simulation model that will be built. In SLAM II simulation networks, tasks are represented by ACTIVITY symbols. These symbols are shaped like arrows. In order to reduce confusion while using the developed flowchart to create the simulation network model, it is useful to number each arrow prior to a task in the flowchart (Figure 8). Although the first task does not have an arrow before it, it is essential that a number is assigned and placed before the first task to denote an ACTIVITY flow. Therefore, these numbered arrows now represent the tasks for project planning. The characteristics of the ACTIVITY nodes include durations of tasks, probabilities of failed tasks having to be repeated, or probabilities of successful tasks. The durations of the tasks were estimated earlier in Section 4.5.

The estimated probabilities of potential Repeat Tasks will be determined in the next step. Due to the variability of the task flow, and constant modification to the flowchart, it is not always possible or convenient to use sequential arrow numbers. It is, therefore, not necessary to emphasize the use of sequential task flow numbers in the flowchart. As may be seen later in the simulation network model, some of these numbers will not be utilized if deemed unnecessary.

It is important to note that the ACTIVITY numbers in the simulation model must correspond with the task arrow numbers within the flowchart to ensure compatibility between the model and the flowchart. Again, as may be viewed later in the simulation network model, there will be situations where arrow task numbers have to be added because one task arrow in the flowchart represents more than one ACTIVITY in the

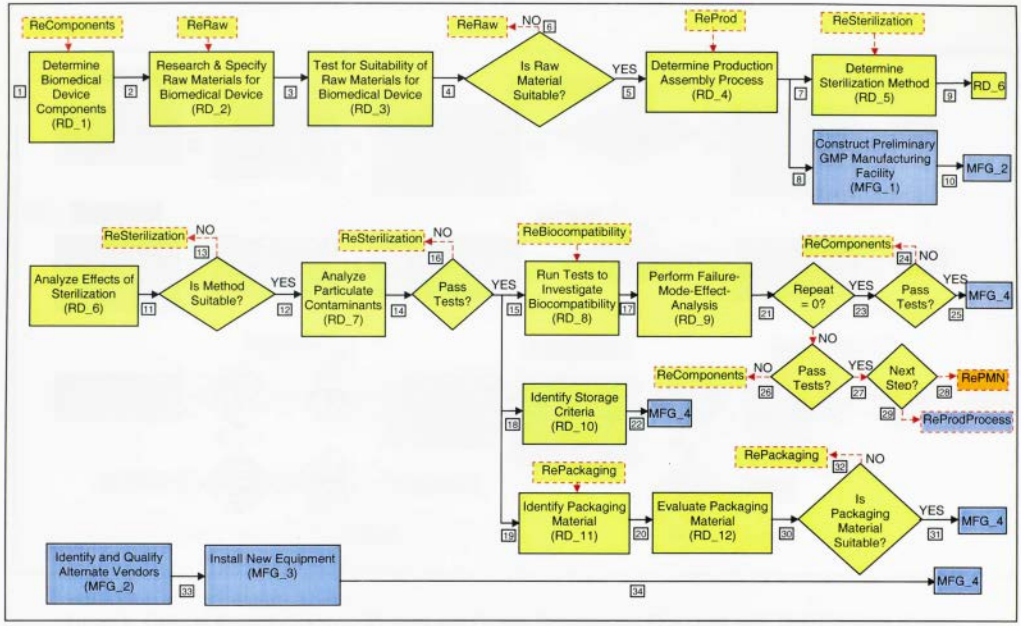

Figure 8: General Biomedical Device Product and Process Development Flowchart with Task Numbers.

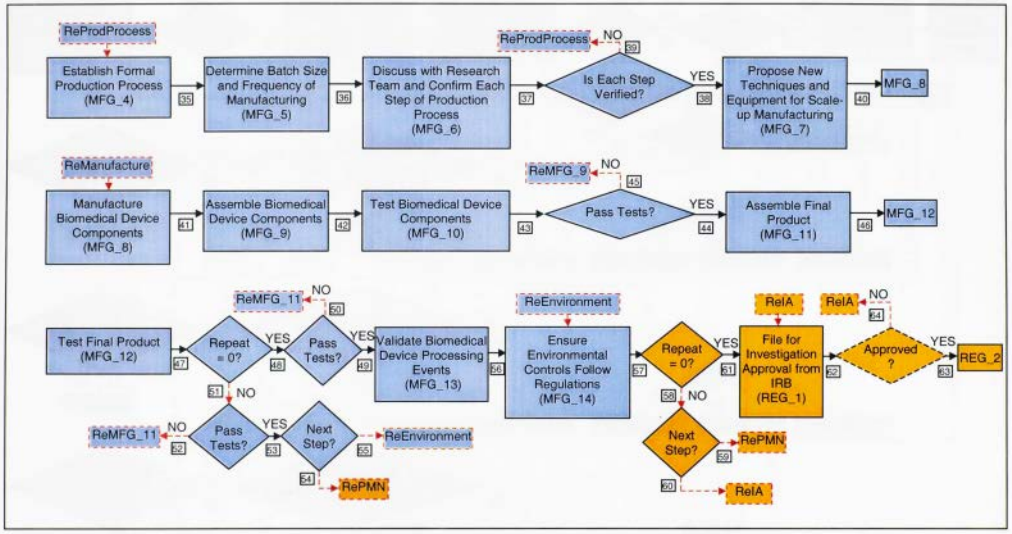

Figure 8: General Biomedical Device Product and Process Development Flowchart with Task Numbers (Cont.).

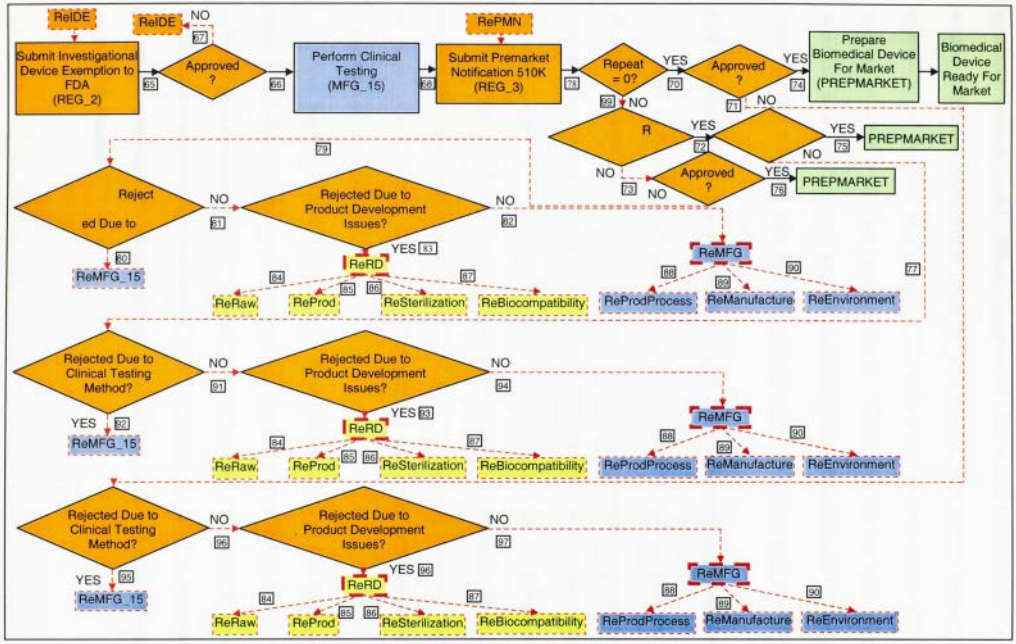

Figure 8: General Biomedical Device Product and Process Development Flowchart with Task Numbers (Cont.).

simulation network model. When a situation like this occurs, all ACTIVITY symbols relating to that task arrow will be given the same number. This usually occurs when the probability and duration for a single task has to be shown as two separate ACTIVITY symbols in order to facilitate repetitive tasks. There may also be cases where the flowchart may show separate task arrows for multiple entity routes but the simulation network model may need only one route, with the entity passing through it repeatedly.

4.10 Estimate Probabilities of Potential Repeat Tasks and Phantom Repeat Tasks

One of the unique advantages of using simulation for project planning is the ability to represent Repeat Tasks and Phantom Repeat Tasks, and to assign uncertainties or probabilities to them. In most project planning and management software currently on the market, this is not possible. For project planning purposes, the probabilities of repeating tasks can be easily modified to decrease as more repetitions occur. This provides the project planner with the distinct advantage of justifying necessary changes in the project plan, as well as estimating the number of times a task will be repeated even before beginning the project.

For simulation modeling purposes, these probabilities can be determined by referencing historical data, speaking to people directly involved in the tasks, and by making logical assumptions. These probabilities can be shown directly on the flowchart, in the simulation model, or in a separate table with the corresponding task arrow number. For space conservation, the probabilities are shown directly in the simulation model, and not in the flowchart.

4.11 Develop Simulation Network Model

The project planning network for biomedical device process development and manufacturing utilizes a variety of nodes and symbols available in the SLAM II language. They include the ASSIGN, ACCUMULATE, COLCT, CREATE, GOON, TEXT and TERMINATE nodes, as well as the ACTIVITY symbols. Except for the TEXT nodes, general combinations of these nodes and symbols have been developed in this research to accommodate biomedical device project planning purposes. The TEXT nodes are excluded from these combinations because they do not affect the running of the simulation, and are only used as "captions" to identify tasks. Each general combination is called a subnetwork. A project planner can either use these subnetworks to develop customized simulation network model to plan for biomedical device product and process development or use the general simulation network model developed in Section 4.11.5, and modify the model to accommodate project uniqueness. Example applications of these subnetworks are presented in the following sections.

4.11.1 "START OF PROJECT" Subnetwork

CREATE and COLCT are the basic nodes and ACTIVITY is the basic symbol used to model the start of a project (Figure 9). The main function of the CREATE node is to generate entities to be routed into the network.

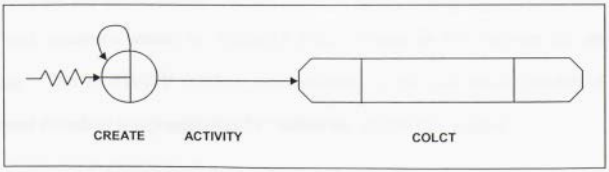

Figure 9: "START OF PROJECT" Subnetwork.

An application of the "START OF PROJECT" subnetwork is shown in Figure 10. For project planning purposes, the time of the first created entity is 0.0, shown above the squiggly line before the CREATE node. For project planning networks, only one entity is created. Therefore, the time between arrivals is 0.0, denoted above the top curve. The value for the maximum number of creations is also set at 1, as shown in the lower left section of the CREATE node. Similarly, the maximum number of entities to be routed out of the node is set at 1, as shown in the right section of the CREATE node.

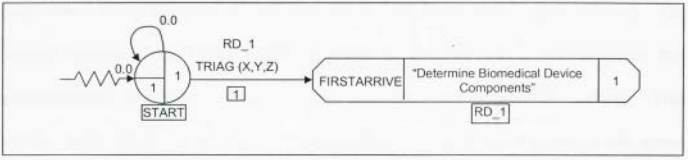

Figure 10: "START OF PROJECT" Subnetwork Application.

Each Primary or Secondary Task is represented by an ACTIVITY symbol and has a specified duration, condition, or both. The duration specifies a time delay for an entity moving through that activity. For project planning purposes, the value of the duration and condition is set as a constant or as a SLAM II random variable. For the "START OF PROJECT" subnetwork in Figure 10, the first task is "Determine Biomedical Device Components". The ACTIVITY symbol utilizes the data collected in Section 4.5. Therefore, the SLAM II random variable of a triangular distribution with a maximum, mode and minimum value, or TRIAG(X,Y,Z), is used as the duration for project planning. The ACTIVITY number, corresponding to the task arrow number in the developed flowchart is represented as "1" within the ACTIVITY symbol.

In project planning, some of the most important performance measures are the estimated start time of a certain task and the project's estimated completion time. The COLCT or Collect Node is used to compile the estimated start times for each predetermined task, as well as the estimated overall project completion time. In order to obtain an estimated earliest completion time for the "Determine Biomedical Device Components" task, FIRSTARRIVE is used in the first column of the COLCT node (Figure 10). In SLAM II, the estimates for the mean and standard deviation values of these observations are automatically recorded and presented in the output summary. The second column of the COLCT node requires an identifier. It is recommended that predetermined task names always be used as inputs for the identifier column. This enables each COLCT node to be later identified in the output summary by its task name. In the third column, "1" represents the maximum number of entities allowed to exit the COLCT node. This number is generally "1", except for cases where an entity is divided into two or more entities to simulate activities being performed concurrently.

It is also very important for the project planner to be able to easily manipulate the variables and probabilities set for the different tasks. For example, it is usually necessary to represent the probability of a task being reworked a third time to be of a lesser value than the probability of the task having to be performed the second time. Therefore, it may be necessary to differentiate an entity arriving into the system for the very first time that has to flow through all tasks, from an entity that is looped back to simulate a Repeat task. The "START OF PROJECT WITH ENTITY ASSIGNMENT" subnetwork (Figure 11), shows a particularly useful combination of CREATE, ASSIGN, GOON, and

COLCT nodes as well as ACTIVITY symbols. The ASSIGN node is utilized when there is a need to set a value for an attribute of an entity passing through it.

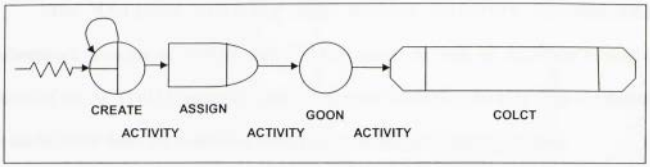

Figure 11: "START OF PROJECT WITH ENTITY ASSIGNMENT" Subnetwork.

In order to assign and differentiate these tasks, the ASSIGN node in "START OF PROJECT WITH ENTITY ASSIGNMENT" subnetwork is given the criterion of ATRIB[1] with the actual numerical value of 1 (Figure 12). ATRIB[1], therefore, represents the type of arriving entity and the actual numerical value of 1 represents an entity flowing through the task from the very beginning of the project.

The GOON node functions as a separator of tasks (Figure 12). It is used to link tasks that are sequential. It is also used when a single task is followed by several tasks that need to be performed simultaneously, in which case the value of the GOON node will be the number of those tasks. The GOON node is also utilized whenever there is a possibility that a task may be repeated due to failure. It is recommended that if the GOON node is used as a link for repeated activities, a "Re" be added to the front of the label to signify this use in the network model.

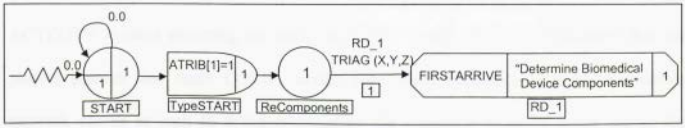

Figure 12: "START OF PROJECT WITH ENTITY ASSIGNMENT" Subnetwork Application.

4.11.2 "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" Subnetwork

The "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" subnetwork consists of GOON and COLCT nodes, as well as ACTIVITY symbols. Some of the ACTIVITY symbols represent Repeat Tasks (Figure 13). This combination is useful when there are sequential tasks and probabilities of repeating tasks.

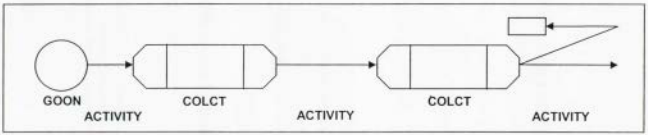

Figure 13: "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" Subnetwork.

For example, in the general biomedical device product and process development flowchart, the task, "Research and Specify Raw Materials for Biomedical Device" is followed by the task, "Test for Suitability of Raw Materials for Biomedical Device." As noted in the flowchart, there is a possibility that the chosen raw material may fail the test, and the task, "Research and Specify Raw Materials for Biomedical Device" will have to be repeated. This application is shown in Figure 14. Figures 15 to 18 show other applications of the "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" subnetwork. In order to collect the number of times a task is repeated, an additional COLCT node is used between the Repeat ACTIVITY symbol and another ACTIVITY symbol directing the entity to a "Re" node. It is recommended that the project planner use these COLCT nodes only when necessary to avoid simulation network clutter as well to avoid overloading the computer memory space during the running of the simulation.

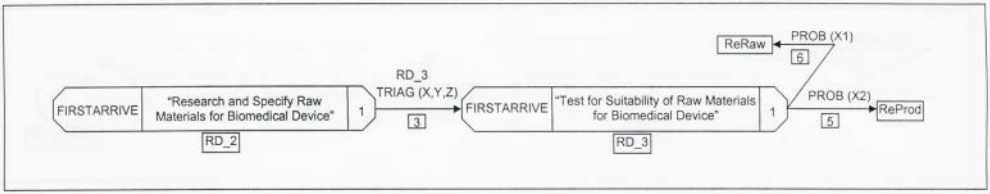

Figure 14: "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" Subnetwork Application 1.

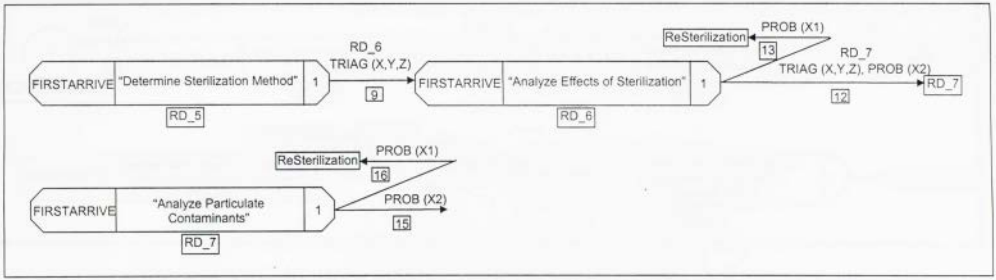

Figure 15: "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" Subnetwork Application 2.

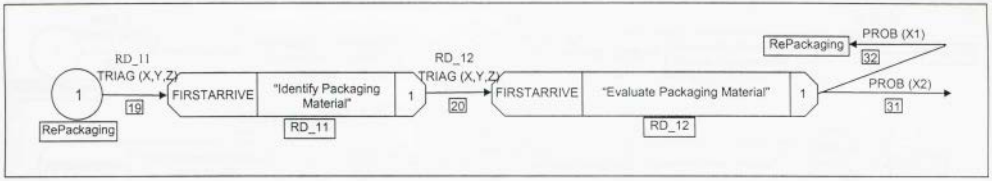

Figure 16: "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" Subnetwork Application 3.

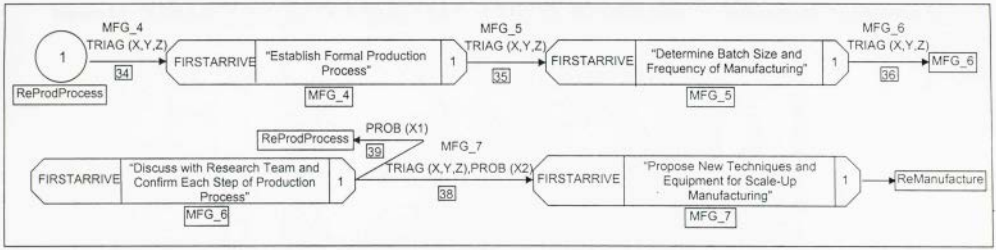

Figure 17: "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" Subnetwork Application 4.

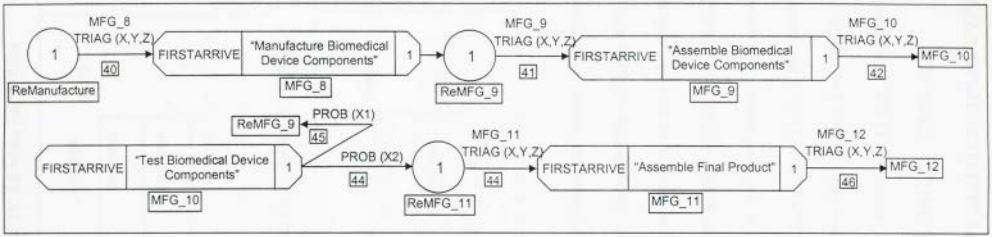

Figure 18: "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" Subnetwork Application 5.

4.11.3 "SPLIT ACTIVITY" Subnetwork

The "SPLIT ACTIVITY" subnetwork consists of a GOON or COLCT node, and multiple ACTIVITY symbols. These combinations are commonly used to cause an entity to divide and flow in separate paths simultaneously to simulate concurrent tasks being performed ("SPLIT ACTIVITY-SIMULTANEOUS FLOW" subnetwork), to direct an entity to a certain path due to a predetermined probability of the entity taking that path ("SPLIT ACTIVITY-PROBABILISTIC FLOW" subnetwork), or to direct an entity to a certain path due to its attribute ("SPLIT ACTIVITY-ATTRIBUTE FLOW" subnetwork). These different subnetworks are shown in Figures 19 to 21. Example applications for these subnetworks are shown in Figures 22 to 27.

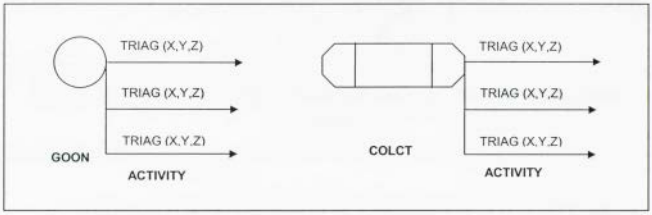

Figure 19: "SPLIT ACTIVITY-SIMULTANEOUS FLOW" Subnetwork.

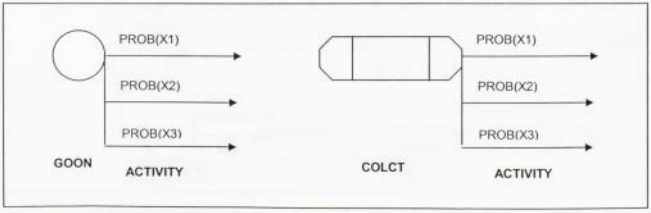

Figure 20: "SPLIT ACTIVITY-PROBABILISTIC FLOW" Subnetwork.

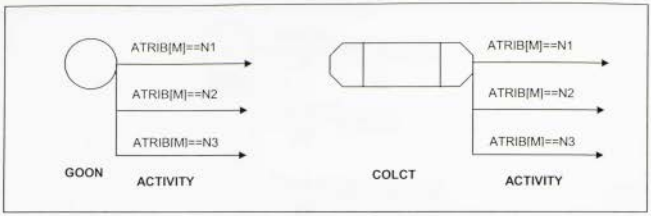

Figure 21: "SPLIT ACTIVITY-ATTRIBUTE FLOW" Subnetwork.

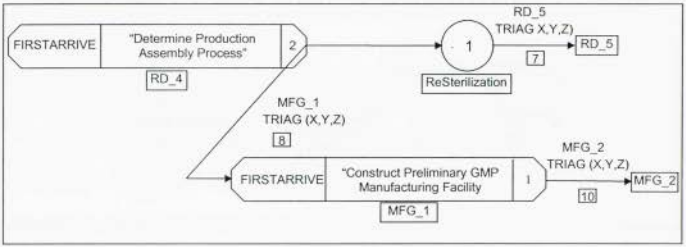

Figure 22: "SPLIT ACTIVITY-SIMULTANEOUS FLOW" Subnetwork Application 1.

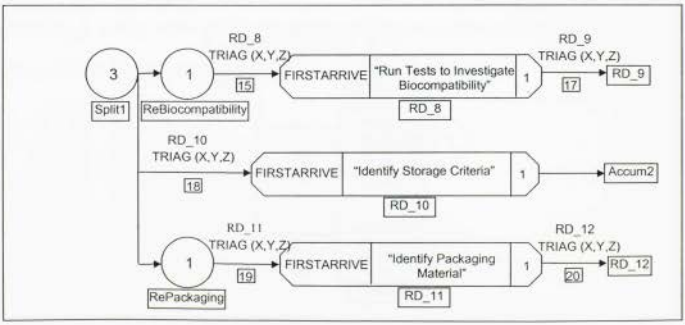

Figure 23: "SPLIT ACTIVITY-SIMULTANEOUS FLOW" Subnetwork Application 2.

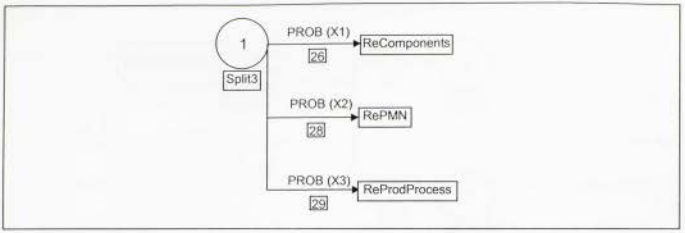

Figure 24: "SPLIT ACTIVITY-PROBABILISTIC FLOW" Subnetwork Application 1.

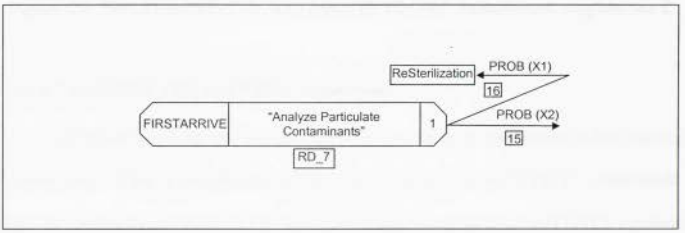

Figure 25: "SPLIT ACTIVITY-PROBABILISTIC FLOW" Subnetwork Application 2.

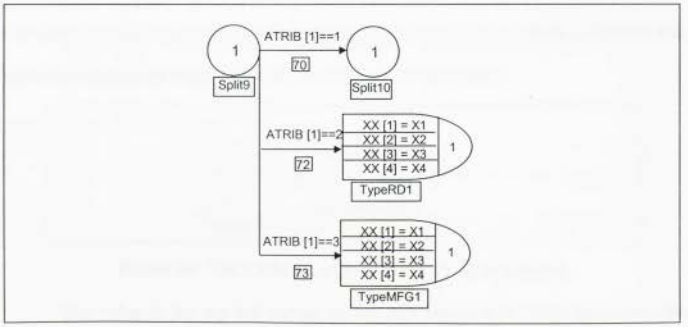

Figure 26: "SPLIT ACTIVITY-ATTRIBUTE FLOW" Subnetwork Application 1.

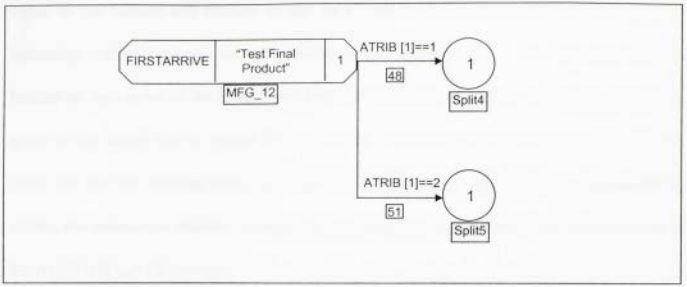

Figure 27: "SPLIT ACTIVITY-ATTRIBUTE FLOW" Subnetwork Application 2.

4.11.4 "ACCUMULATE ACTIVITY" Subnetwork

In project planning, certain tasks commonly need to be performed before starting another task. This is modeled using the "ACCUMULATE ACTIVITY" subnetwork. The "ACCUMULATE ACTIVITY" subnetwork consists of several ACTIVITY symbols entering a single ACCUMULATE node (Figure 28). The ACCUMULATE node is used to route one exiting entity from a group of incoming entities. Therefore, in project planning, it is only when a defined number of preceding tasks have been completed that the node releases one entity so that the next task can be performed.

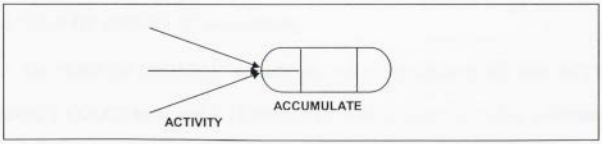

Figure 28: "ACCUMULATE ACTIVITY" Subnetwork.

The value in the top-left section of the ACCUMULATE node determines the required number of incoming entities to release the node for the first time whereas the

value in the bottom left section of the ACCUMULATE node specifies the number of incoming entities required for subsequent releases (Figure 29). The criterion "LAST", located in the center of the node, specifies that the attributes of the last arriving entity be given to the entity that is routed from the node. Therefore, this criterion stores the time value for the last arriving entity to that node. A single exiting entity is represented by setting the maximum number of outgoing branches, located in the right-most column of the ACCUMULATE node, at "1."

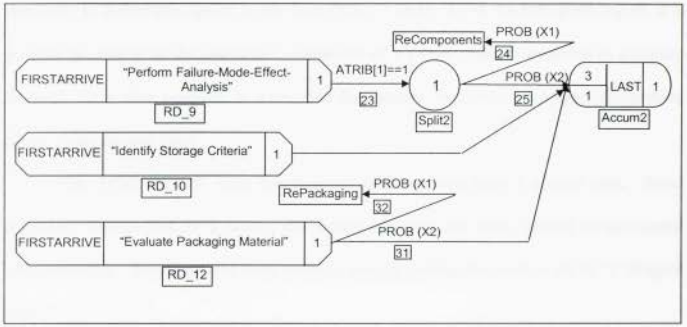

Figure 29: "ACCUMULATE ACTIVITY" Subnetwork Application.

4.11.5 "END OF PROJECT" Subnetwork

The "END OF PROJECT" subnetwork is a combination of the final ACTIVITY symbol(s), a COLCT node and a TERMINATE node (Figure 30). This combination is used at the end of a simulation network model.

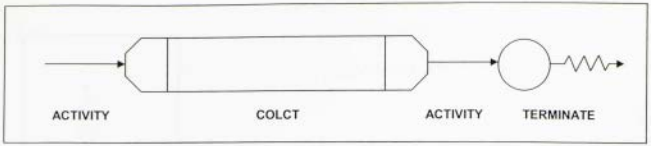

Figure 30: "END OF PROJECT" Subnetwork.

SLAM II has the capability of providing the output data in the form of a histogram report. In order to obtain a histogram report in the output summary, it is necessary to define this option in the final COLCT node. From the histogram report, it is possible to determine the estimated probability of a project being completed in a certain duration. It is also possible to determine the relative frequency of project completion times, given several runs.

The TERMINATE node functions to delete entities from a project plan. Since one entity was created for a project simulation run, only one entity should be terminated after every run. Therefore, the total count of entities exiting this node is set at "1" (Figure 31).

4.11.6 TEXT Node

The TEXT node is used to match tasks with their durations. Therefore, this node is usually placed above the ACTIVITY node, and is provided the labels specified in Column 4.4 of Table 5. The labels within this column are used because they capture each task within the biomedical device product and process development. The use of this node does not affect the running of the simulation model.

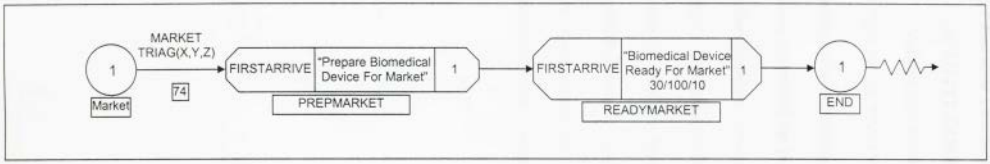

Figure 31: "END OF PROJECT" Subnetwork Application.

4.11.7 Example Combinations of "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" and "SPLIT ACTIVITY" Subnetworks

Various combinations of "COLLECT ACTIVITY AND REPEAT ACTIVITY" and "SPLIT ACTIVITY" subnetworks are used to assign different probabilities to different tasks depending on the attribute of that entity. For example, if an application has been submitted for Premarket Notification and denied by the FDA due to a Research and Development problem, the entity is assigned ATRIB[1]=2, and is repeated at "ReRD". Similarly, if the application was denied by the FDA due to a Manufacturing problem, the entity is assigned ATRIB[1]=3, and is repeated at "ReMFG." As the entities are rerouted back to repeat the problem tasks, the probabilities of task repetition can be easily manipulated by using ASSIGN nodes with variables that represent these probabilities. An example application of this can be seen in Figure 32 and Figure 33.

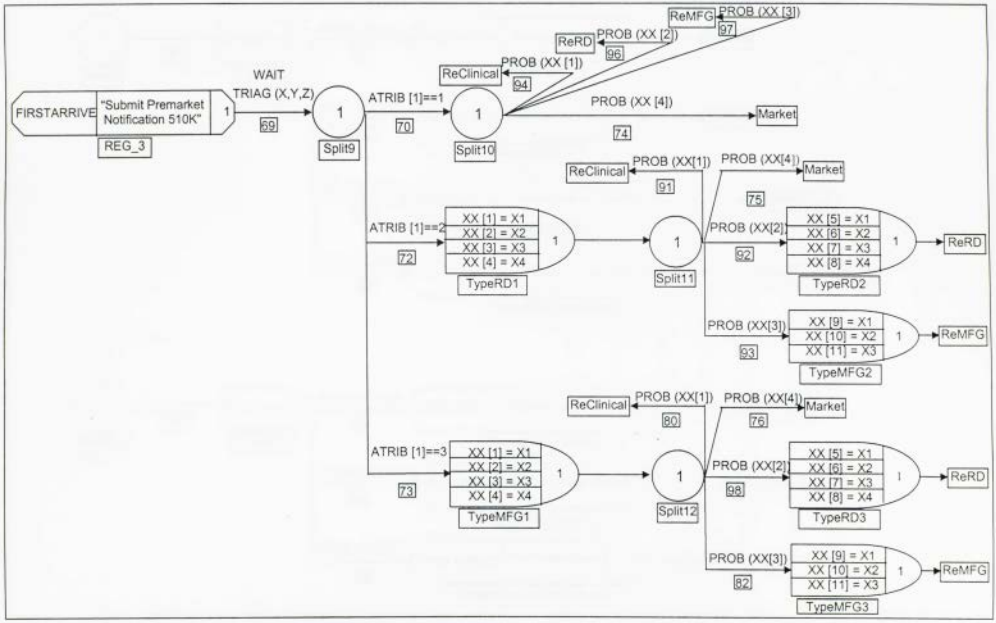

Figure 32: Example Combination of "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" and "SPLIT ACTIVITY" Subnetworks 1.

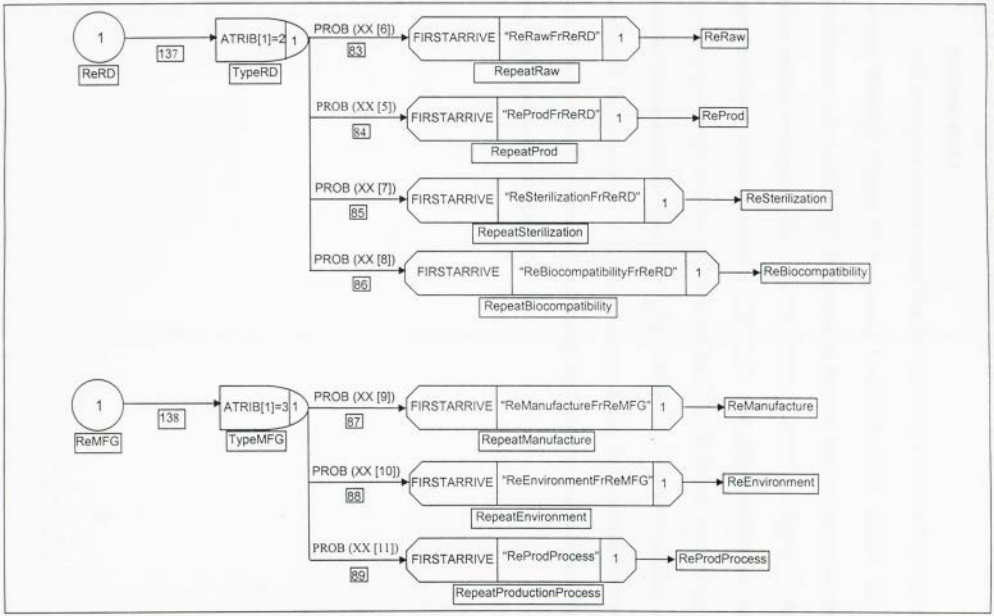

Figure 33: Example Combination of "COLLECT ACTIVITY AND REPEAT ACTIVITY INFORMATION" and "SPLIT ACTIVITY" Subnetworks 2.

4.11.8 General Biomedical Device Product and Process Development Simulation Network Model

The simulation network model was developed based on the information from the previous flowchart (Figure 8) for general biomedical device product and process development. An overview of the simulation network model for general biomedical device product and process development is shown in Figure 34. Figure 35 shows an exploded version of the simulation network model. The product planner may choose to develop a new simulation network from scratch utilizing the BOPP methodology and the provided subnetworks or modify the general biomedical device simulation network model to fit the uniqueness of a biomedical device. A detailed example application of the general biomedical device product and process development simulation network model template is addressed in Chapter 5.

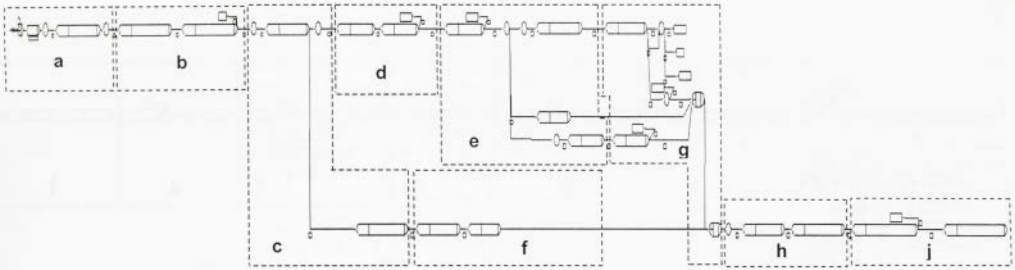

Figure 34: Simulation Network Model for General Biomedical Device Product and Process Development - Overview.

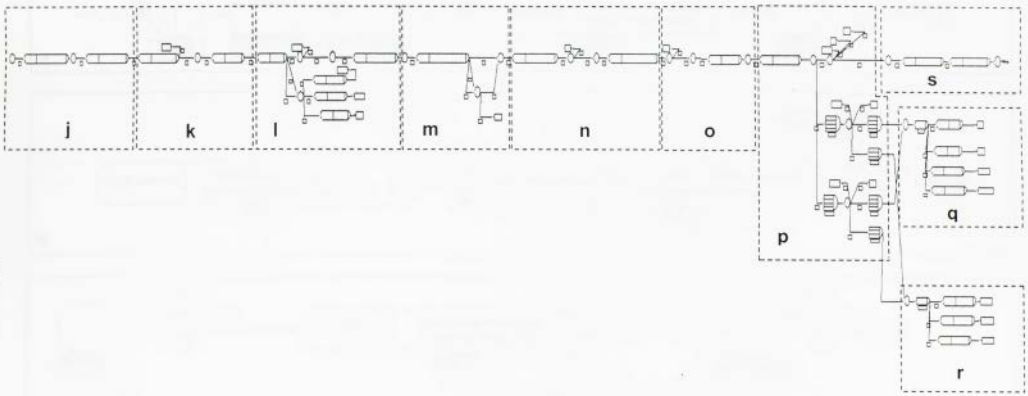

Figure 34: Simulation Network Model for General Biomedical Device Product and Process Development – Overview (Cont.).

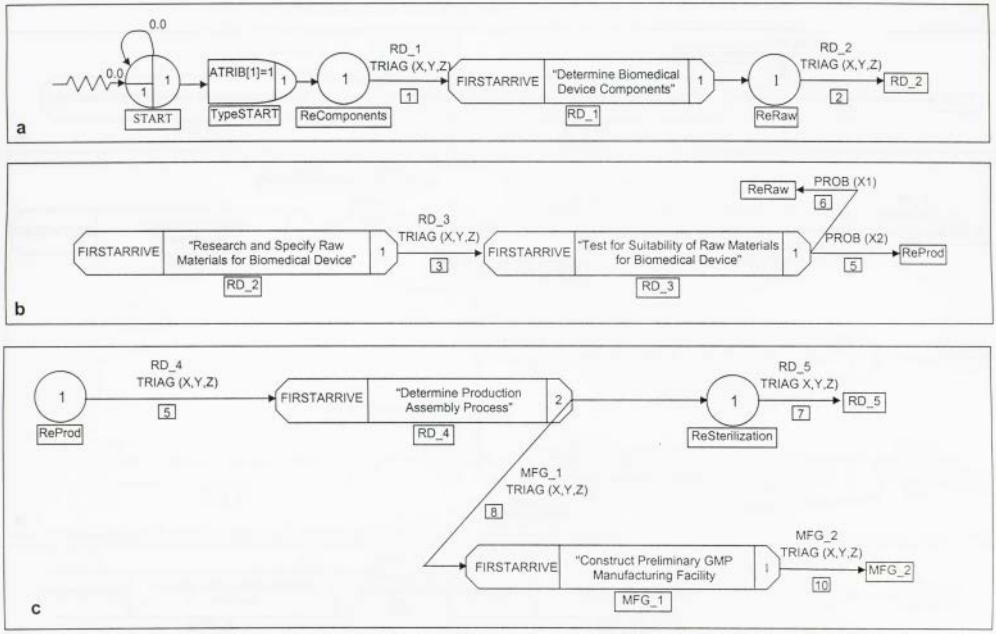

Figure 35: Simulation Network Model for General Biomedical Device Product and Process Development – Exploded.

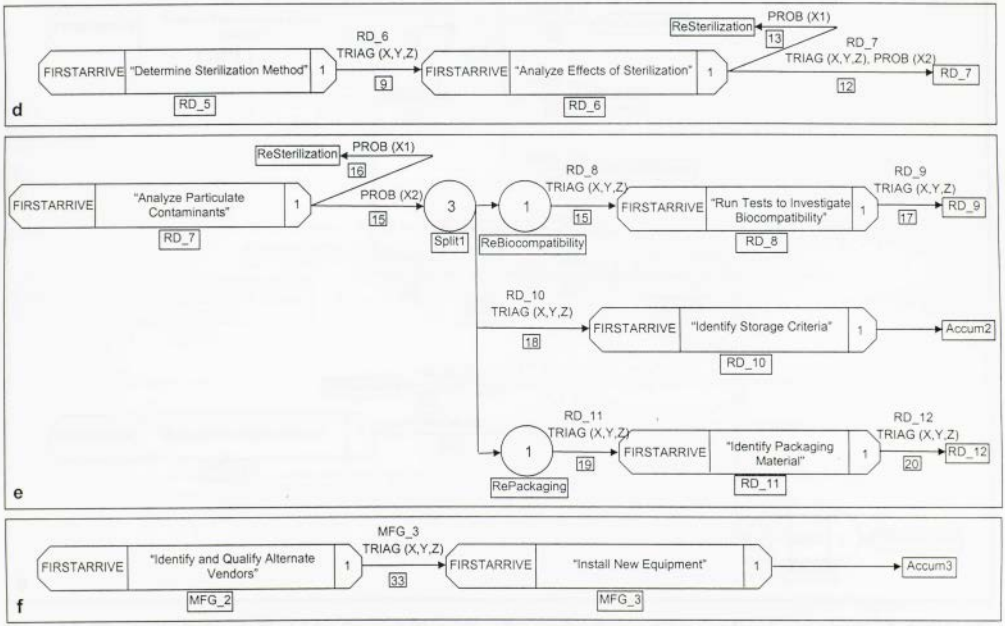

Figure 35: Simulation Network Model for General Biomedical Device Product and Process Development – Exploded (Cont.).

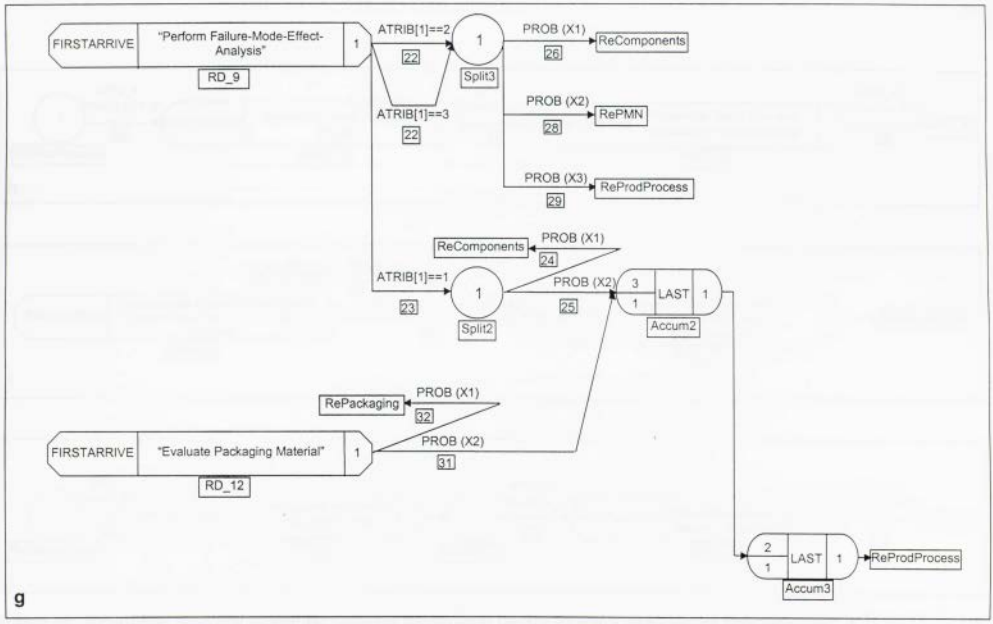

Figure 35: Simulation Network Model for General Biomedical Device Product and Process Development – Exploded (Cont.).

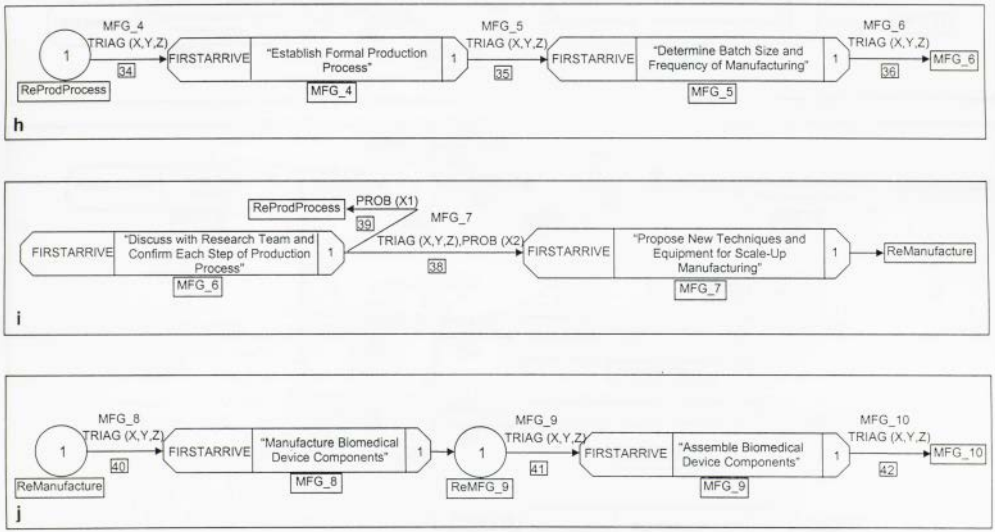

Figure 35: Simulation Network Model for General Biomedical Device Product and Process Development – Exploded (Cont.).

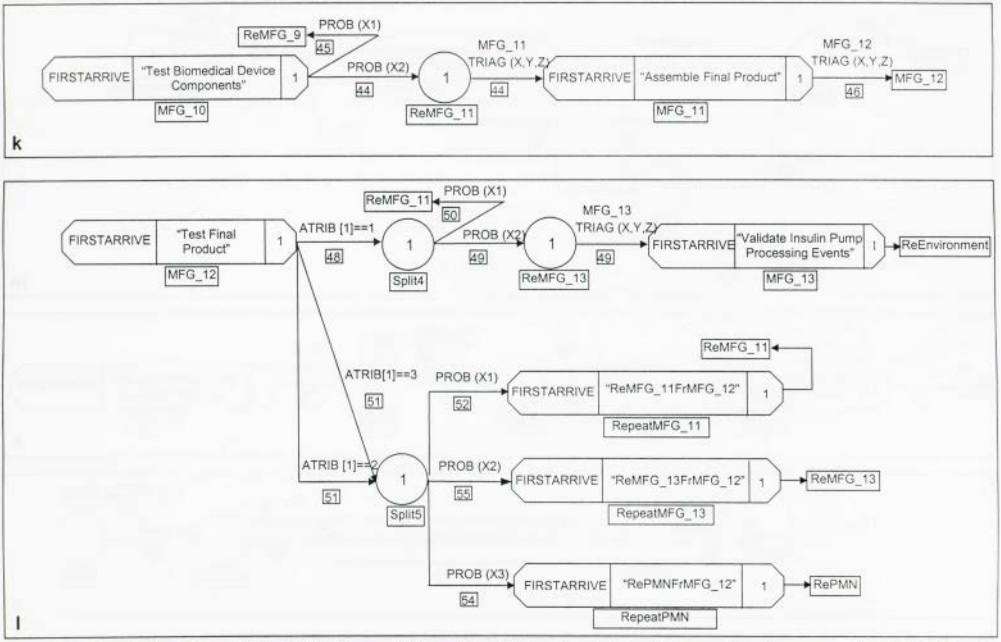

Figure 35: Simulation Network Model for General Biomedical Device Product and Process Development – Exploded (Cont.).

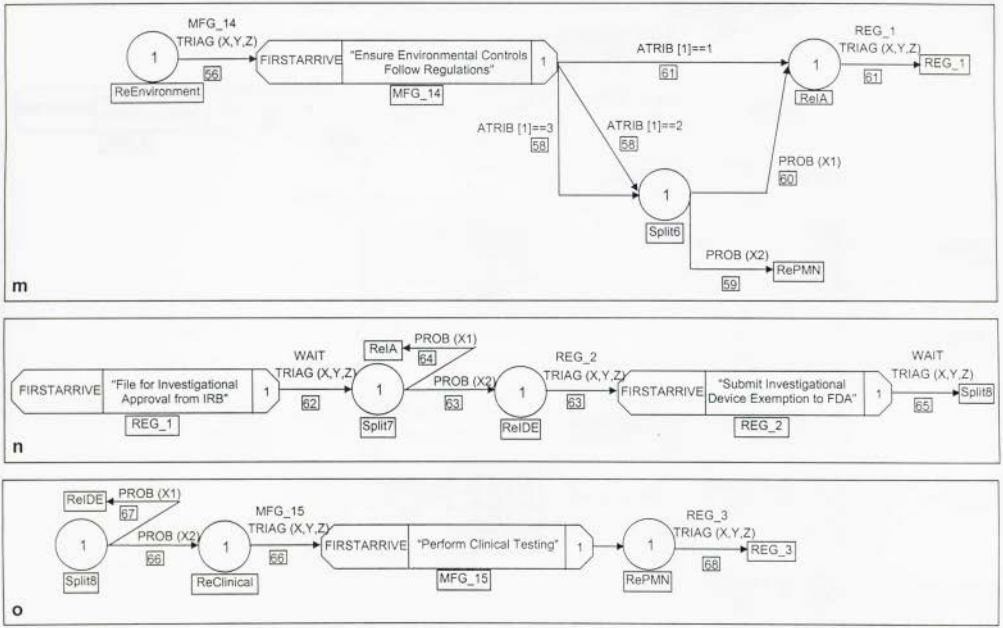

Figure 35: Simulation Network Model for General Biomedical Device Product and Process Development – Exploded (Cont.).

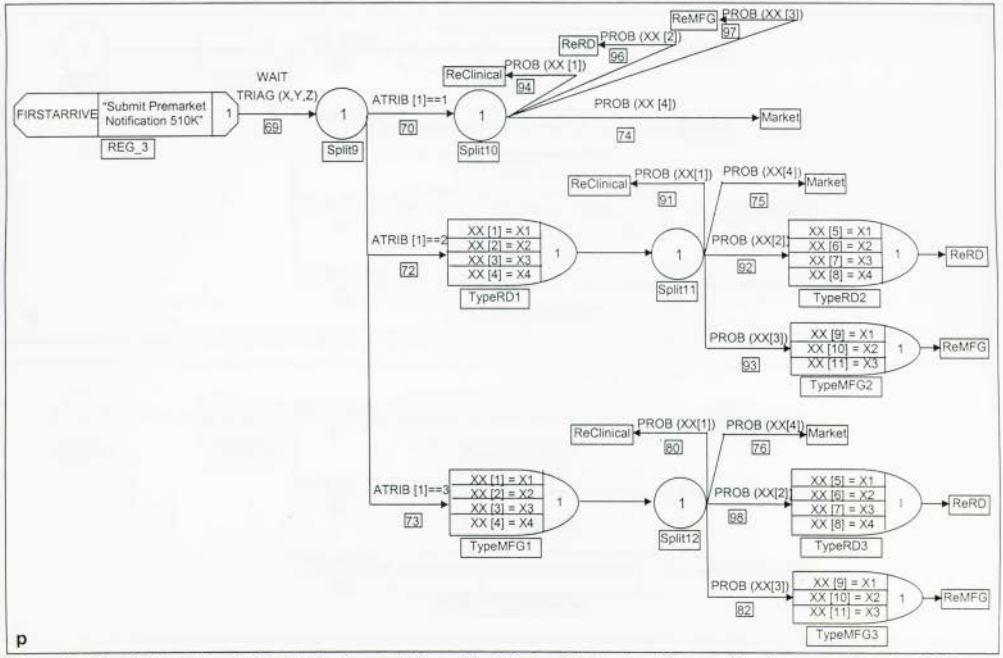

Figure 35: Simulation Network Model for General Biomedical Device Product and Process Development – Exploded (Cont.).

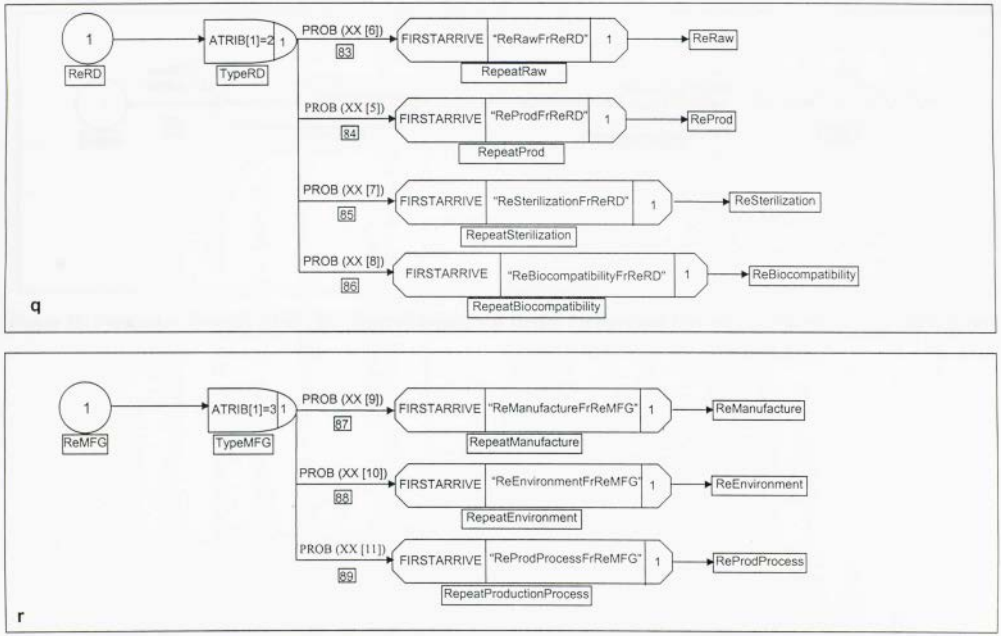

Figure 35: Simulation Network Model for General Biomedical Device Product and Process Development – Exploded (Cont.).

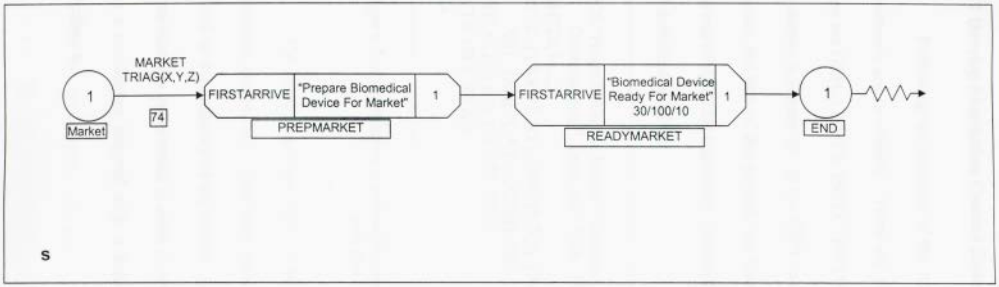

Figure 35: Simulation Network Model for General Biomedical Device Product and Process Development – Exploded (Cont.).

4.12 Develop Simulation Control Statements

Following the creation of the simulation network model, the simulation Control Statements are developed. There are six basic control statements for project planning. They are GEN, LIMITS, INTLC, INITIALIZE, NETWORK, and FIN. These statements are shown in Figure 36. In the GEN statement, the inputs include the name of the project planner, the title of the project, the date the project is created, and the number of runs. The rest of the GEN statement, "Attempt Execution" and "Warn of Destroyed Entities", is left defaulted at "Yes."

```
GEN,"Project Planner Name","General Biomedical Device Product and Process
     Development", Date, M1, YES, YES;
LIMITS,11,,,3;
INTLC,{{XX[1], X1},{XX[2], X2},{XX[3], X3},{XX[4], X4}{XX[5], X5},{XX[6],
     X6}, {XX[7], X7},{XX[8], X8},{XX[9], X9},{XX[10], X10},{XX[11], X11}};
INITIALIZE,0.0, M2,NO,,YES;
NETWORK,READ;
FIN;
```

Figure 36: Simulation Control Statements for General Biomedical Device Product and Process Development.

The most important input in the GEN Statement is the number of runs of the simulation model, M1. This input determines the number of replications for simulation as well as the accuracy of the results. Kelton et al. (1998) recommend that an initial set of replications, n_0, is made in order to obtain a sample average, X, a standard deviation, s, and a confidence interval with a half-width, h_0. The following formula is used to calculate h_0:

$$h_0 = t_{n_0-1,1-\alpha/2}\frac{s}{\sqrt{n_0}}$$

where t is the t-statistic with n - 1 degrees of freedom and a probability level of 1 - $\alpha/2$.

It is recommended that the model first be simulated for 20 runs. Having analyzed the results to obtain a confidence interval with a certain half-width, the project planner may choose to increase or reduce this half-width if deemed necessary to obtain more desirable results. This will require a manipulation of the number of runs in the simulation. The formula to determine the required number of runs to achieve a certain half-width in a confidence interval will be shown in Section 4.14.

The LIMITS statement (Figure 36) allows the project planner to set the maximum allowable limits for global variables and attributes. Since the simulation model for general biomedical device product and process development planning contains eleven XX[] global variables and three ATRIB[] attribute variables, the inputs for the maximum allowable limits for these variables are 11 and 3, respectively.

The INTLC statement assigns initial values to the XX[] global variables. Since these global variables are used in the simulation model to represent the possibility of repeating tasks, the values for these variables are set according to the probability of repeating those tasks for the first time. For example, the project planner can give the global variable, XX[1] a probability of X1.

In the INTLC statement, the variables, XX[1], XX[2], XX[3], and XX[4] represent the initial probabilities of looping back in the simulation model from the submission of PMN (REG_3) to the clinical testing (ReMFG_19) task, the Manufacturing phase (ReMFG) and the Research and Development phase (ReRD), respectively. The

variables, XX[5], XX[6], XX[7], and XX[8] represent the characteristics of an entity that is looped back to the "ReRD" phase (ATRIB[1]==2) and variables XX[9], XX[10], and XX[11] represent the characteristics of an entity that is looped back to the "'ReMFG" phase (ATRIB[1]==3). Therefore, the variables, XX[5], XX[6], XX[7], and XX[8], represent the initial probabilities of looping back from the submission of PMN (REG_3) to the determination of raw materials (ReRaw), the determination of product assembly process (ReProd), determination of sterilization method (ReSterilization), and determination of biocompatibility (ReBiocompatibility). The variables, XX[9], XX[10], and XX[11] represent the initial probabilities of looping back from the submission of PMN (REG_3) to the manufacturing, assembling, and testing of biomedical device components (ReManufacture), determination of environmental controls (ReEnvironment), and determination of formal production process (ReProdProcess).

The INITIALIZE Statement (Figure 36) is used to set the beginning and ending times for each simulation run. Since the simulation network model was created to start at time 0.0, the begin time of the simulation run is set to be 0.0. The end time of a simulation run, M2, differs from project to project and is obtained using trial and error. The project planner should set this time by estimating the longest amount of time the whole project could possibly take. If the simulation run takes longer than this input, the results will either give an error during the simulation run, or give no data at all in the final few COLCT node results. Therefore, the project planner can modify the INITIALIZE statement to lengthen the simulation run. The project planner should choose "No" in the "Clear Statistics Between Runs" section. This will provide the project planner with the

average results of all the runs and will provide a histogram report of all runs that can be used for further analysis.

The NETWORK and FIN Statements must be included to run the model. The NETWORK Statement is defaulted at option "READ." The FIN Statement does not require any input from the project planner and merely specifies the end of the CONTROL statements.

4.13 Run Simulation Model

Once the input for the Control Statement has been completed, the simulation model is run. As mentioned in the previous section, it is recommended that the model first be simulated for 20 runs. After analyzing the results of these 20 runs, depending on the desired accuracy of the results, more runs may be made to reduce the half-width confidence interval.

4.14 Analyze Results

The simulation results will provide a summary of the requested runs. Figure 37 shows an example of the AweSim Summary Report for the general biomedical device product and process development simulation network model developed previously. The Summary Report includes the day, date, time and year the report is printed, the title of the simulation project, the name of the project planner or modeler, the date the model was created, the name of the scenario, number of runs, current simulation time, and the time that the statistics were last cleared. Within the Observed Statistics Report section of the Summary Report are the task labels, average across all runs of the mean values, standard

** AweSim SUMMARY REPORT **
Day Date Time Year
Simulation Project : General Biomedical Device Product and Process Development
Modeler : Project Planner
Date :
Scenario : BASECASE

Run number M of M
Current simulation time :
Statistics cleared at time :

** OBSERVED STATISTICS REPORT for scenario BASECASE **

Label	Mean Value	Standard Deviation	No. of Observations	Minimum Value	Maximum Value
Determine Biomedical Device Components					
Research and Specify Raw Materials for Biomedical Device					
Test for Suitability of Raw Materials for Biomedical Device					
Determine Production Assembly Process					
Determine Sterilization Method					
Analyze Effects of Sterilization					
Analyze Particulate Contaminants					
Run Tests to Investigate Biocompatibility					
Perform Failure-Mode-Effect-Analysis					
Identify Storage Criteria					
Identify Packaging Material					
Evaluate Packaging Material					
Construct Preliminary GMP Manufacturing Facility					

Figure 37: Results of Simulation Run – Observed Statistics Section.

Label	Mean Value	Standard Deviation	No. of Observations	Minimum Value	Maximum Value
Identify and Qualify Alternate Vendors					
Install New Equipment					
Establish Formal Production Process					
Determine Batch Size and Frequency of Manufacturing					
Discuss with Research Team and Confirm Each Step of Production Process					
Propose New Techniques and Equipment for Scale-Up Manufacturing					
Manufacture Biomedical Device Components					
Assemble Biomedical Device Components					
Test Biomedical Device Components					
Assemble Final Product					
Test Final Product					
Validate Insulin Pump Processing Events					
Ensure Environmental Controls Follow Regulations					
File For Investigational Approval by IRB					
Submit Investigational Device Exemption to FDA					
Perform Clinical Testing					
Submit Premarket Notification 510K					
Prepare Biomedical Device For Market					
Biomedical Device Ready for Market					

Figure 37: Results of Simulation Run – Observed Statistics Section (Cont.)

Label	Mean Value	Standard Deviation	No. of Observations	Minimum Value	Maximum Value
ReMFG_11FrMFG_12					
ReMFG_13FrMFG_12					
RePMNFrMFG_12					
ReRawFrReRD					
ReProdFrReRD					
ReSterilizationFrReRD					
ReBiocompatibilityFrReRD					
ReManufactureFrReMFG					
ReEnvironmentFrReMFG					
ReProdProcessFrReMFG					

Figure 37: Results of Simulation Run – Observed Statistics Section (Cont.)

deviations, and number of observations, as well as the minimum and maximum time values collected by the COLCT nodes in the simulation network.

The "Mean Value" column (Figure 37) provides the average completion time for each task. The "Standard Deviation" column provides the standard deviation for each task. The "No. of Observations" column denotes the number of times each task is performed. If a COLCT node was used to collect the observations for a Repeat Task from a particular task, the number of times the task is repeated is included within this column. For example, in the general simulation network model, the COLCT node with the identifier of "ReRawFrReRD" will provide the number of times an entity flows

between "ReRaw" and "ReRD." Therefore, it denotes the number of times the entity arrives from "ReRD" to "ReRaw" to be repeated.

The results of the last run will provide a histogram report that is useful for analysis. Through this histogram report , it is possible to determine the probability of a task being completed by a certain time.

Since only one entity was created in the CREATE node, only one entity should exit the simulation system. Therefore, the number of observations for the final COLCT node, "Biomedical Device Ready For Market" should equal the total number of runs specified in the GEN statement within the Control Statements. The gray area in Figure 37 should be checked for this equality after each simulation run.

If the half-width of the confidence interval is considered too large, a new half-width, h, is chosen. The following formula is used to estimate a more appropriate sample size, n:

$$n \approx n_0 \cdot \frac{h_0^2}{h^2}$$

CHAPTER 5

EXAMPLE APPLICATION

This chapter describes the planning and management of a project to develop an external insulin pump, using the methodology described in the previous chapter. There are two type of insulin pumps, implantable and external. The external insulin pump was chosen for this project due to the availability of information on this biomedical device.

5.1 Collect Data

An extensive literature search was conducted to gather information on the functions, components, product and process development methods, and FDA regulations related to the external insulin pump. Although sufficient documentation exists regarding the functions and components of the insulin pump, no public literature was found detailing the product and process development of the pump. Therefore, the general biomedical device process development and manufacturing model developed in the previous chapter was used, along with practical experience gained while working with these pumps. Experts in the insulin pump manufacturing area were also consulted to provide and verify the information needed to develop the project plan.

An insulin pump is a high-technology medical device used for the treatment of insulin-dependent diabetes. Users of external insulin pumps set "basal" and "bolus" doses of insulin. Insulin pumps are programmed to provide "basal" doses continuously during the day, whereas "bolus" doses are given at meal times and at times when blood sugar levels are extremely high (Hitchcock, 2000).

An insulin pump is attached to the human body through a catheter (a flexible plastic tubing) with a needle inserted under the skin near the abdomen. The pump is approximately $2" \times 3" \times 1"$ and weighs between 3 and 6 ounces. Typical top-level insulin pump components include a solenoid motor, pump case, window panel, electronics board or microcomputer and computer software, mechanical driver arm, lead screw, reservoir converter, luer neck lever, battery compartment, and syringe, as shown in Figures 38 and 39 (Minimed™ User's Guide; J. Livingston, personal communication, June 19, 2000). However, the locations of the solenoid motor and electronics board were approximated due to information unavailability.

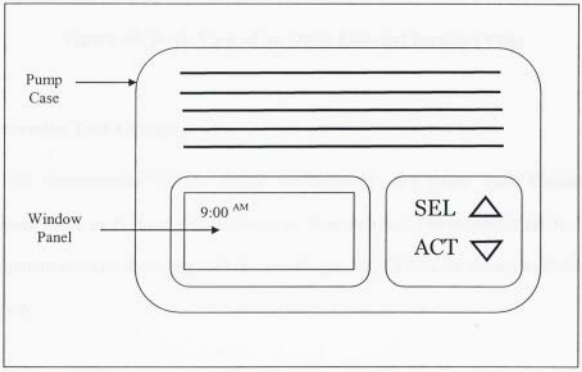

Figure 38: Front View of an External Insulin Pump.

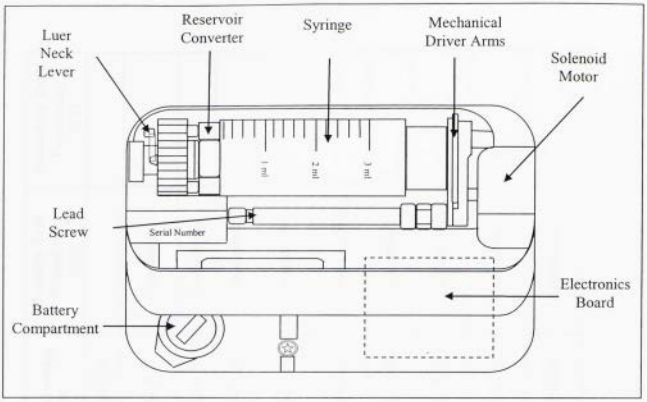

Figure 39: Back View of an Open External Insulin Pump.

5.2 Determine Task Groups

As recommended in the BOPP methodology, the major Task Groups were determined to be in Product Development or Research and Development (RD), Process Development or Manufacturing (MFG), and Regulatory (REG), as shown in Column 5.2 in Table 6.

5.3 Determine Primary Tasks

The Primary Tasks in the general flowchart developed in the methodology were considered applicable for the product and process development of an insulin pump. Therefore, the same Primary Tasks were utilized and given unique labels for easy identification, as shown in Column 5.3 in Table 6.

Table 6: Insulin Pump Project Planning Task Groups and Precedences Summary.

Task Group (5.2)	Primary Task (5.3)	Secondary Task (5.4)	Duration (weeks) (5.5)	Primary Task Precedence (5.6)	Secondary Task Precedence (5.7)
RD	Determine Insulin Pump Components (Components)	None (RD_1)	TRIAG(4,5,6)		
	Identify Raw Materials (Raw)	Research and Specify Raw Materials for Solenoid Motor (RD_2)	TRIAG(2,5,6)	Components	
		Research and Specify Raw Materials for Syringe (RD_3)	TRIAG(1,3,6)	Components	
		Research and Specify Raw Materials for Pump Case (RD_4)	TRIAG(3,5,6)	Components	
		Research and Specify Raw Materials for Window Panel (RD_5)	TRIAG(2,3,5)	Components	
		Research and Specify Raw Materials for Mechanical Driver Arm (RD_6)	TRIAG(4,6,8)	Components	
		Research and Specify Raw Materials for Lead Screw (RD_7)	TRIAG(1,5,9)	Components	
		Research and Specify Raw Materials for Reservoir Converter (RD_8)	TRIAG(2,6,7)	Components	
		Research and Specify Raw Materials for Luer Neck Lever (RD_9)	TRIAG(1,4,9)	Components	
		Research and Specify Raw Materials for Battery Compartment (RD_10)	TRIAG(2,4,5)	Components	

Table 6: Insulin Pump Project Planning Task Groups and Precedences Summary (Cont.).

Task Group (5.2)	Primary Task (5.3)	Secondary Task (5.4)	Duration (weeks) (5.5)	Primary Task Precedence (5.6)	Secondary Task Precedence (5.7)
RD (Cont.)		Develop Code for Software (RD_11)	TRIAG(7,8,9)	Components	
		Test for Suitability of Raw Materials for Solenoid Motor (RD_12)	TRIAG(3,5,6)		RD_2
		Test for Suitability of Raw Materials for Syringe (RD_13)	TRIAG(1,4,5)		RD_3
		Test for Suitability of Raw Materials for Pump Case (RD_14)	TRIAG(2,4,5)		RD_4
		Test for Suitability of Raw Materials for Window Panel (RD_15)	TRIAG(3,4,8)		RD_5
		Test for Suitability of Raw Materials for Mechanical Driver Arm (RD_16)	TRIAG(1,4,8)		RD_6
		Test for Suitability of Raw Materials for Lead Screw (RD_17)	TRIAG(3,5,6)		RD_7
		Test for Suitability of Raw Materials for Reservoir Converter (RD_18)	TRIAG(2,5,8)		RD_8
		Test for Suitability of Raw Materials for Luer Neck Lever (RD_19)	TRIAG(2,3,4)		RD_9
		Test for Suitability of Raw Materials for Battery Compartment (RD_20)	TRIAG(3,7,8)		RD_10
		Test Software Code (RD_21)	TRIAG(2,3,5)		RD_11

Table 6: Insulin Pump Project Planning Task Groups and Precedences Summary (Cont.).

Task Group (5.2)	Primary Task (5.3)	Secondary Task (5.4)	Duration (weeks) (5.5)	Primary Task Precedence (5.6)	Secondary Task Precedence (5.7)
RD (Cont.)	Determine Production Assembly Process (Prod)	None (RD_22)	TRIAG(5,7,8)	Raw	
	Determine and Test Sterilization Method (Sterilization)	Determine Sterilization Method (RD_23)	TRIAG(5,7,8)	Prod	
		Analyze Effects of Sterilization (RD_24)	TRIAG(2,5,6)		RD_23
		Analyze Particulate Contaminants (RD_25)	TRIAG(2,4,6)		RD_24
	Determine Biocompatibility (Biocompatibility)	Run Tests To Investigate Biocompatibility (RD_26)	TRIAG(1,5,6)	Sterilization	
		Perform Failure-Mode-Effect Analysis (RD_29)	TRIAG(2,5,8)		RD_26
	Identify Storage Criteria (Storage)	None (RD_27)	TRIAG(1,2,3)	Sterilization	
	Determine Packaging Material (Packaging)	Identify Packaging Material (RD_28)	TRIAG(1,2,3)	Sterilization	
		Evaluate Packaging Material (RD_30)	TRIAG(1,2,3)		RD_28
MFG	Construct Preliminary GMP Manufacturing Facility (GMP)	None (MFG_1)	TRIAG(12,13,15)	Prod	
	Identify and Qualify Alternate Vendors (Vendor)	None (MFG_2)	TRIAG(4,5,6)	GMP	
	Install New Equipment (Equipment)	None (MFG_3)	TRIAG(3,4,5)	Vendor	
	Establish Formal Production Process (ProdProcess)	Establish Formal Production Process (MFG_4)	TRIAG(5,6,7)	Biocompatibility, Packaging, Equipment	

Table 6: Insulin Pump Project Planning Task Groups and Precedences Summary (Cont.).

Task Group (5.2)	Primary Task (5.3)	Secondary Task (5.4)	Duration (weeks) (5.5)	Primary Task Precedence (5.6)	Secondary Task Precedence (5.7)
MFG (Cont.)		Determine Batch Size and Frequency of Manufacturing (MFG_5)	TRIAG(1,3,5)		MFG_4
		Discuss with Research Team and Confirm Each Step of Production Process (MFG_6)	TRIAG(2,3,4)		MFG_5
		Propose New Techniques and Equipment for Scale-up Manufacturing (MFG_7)	TRIAG(3,6,10)		MFG_6
	Manufacture, Assemble, and Test Insulin Pump Components (Manufacture)	Manufacture Insulin Pump Components (MFG_8)	TRIAG(7,8,12)	ProdProcess	
		Assemble Solenoid Motor (MFG_9)	TRIAG(2,7,9)		MFG_8
		Test Solenoid Motor (MFG_10)	TRIAG(1,5,7)		MFG_9
		Assemble Electronics Board (MFG_11)	TRIAG(2,5,6)		MFG_10
		Test Electronic Board (MFG_12)	TRIAG(4,6,8)		MFG_11
		Assemble Solenoid Motor and Electronics Board on Pump Case (MFG_13)	TRIAG(3,6,7)		MFG_12
		Test Solenoid Motor and Electronics Board on Pump Case (MFG_14)	TRIAG(1,4,5)		MFG_13
		Assemble Final Product (MFG_15)	TRIAG(2,3,4)		MFG_14
		Test Final Product (MFG_16)	TRIAG(2,4,5)		MFG_15
		Validate Insulin Pump Processing Events (MFG_17)	TRIAG(3,6,7)		MFG_16

Table 6: Insulin Pump Project Planning Task Groups and Precedences Summary (Cont.).

Task Group (5.2)	Primary Task (5.3)	Secondary Task (5.4)	Duration (weeks) (5.5)	Primary Task Precedence (5.6)	Secondary Task Precedence (5.7)
MFG (Cont.)	Ensure Environmental Controls Follow Regulations (Environment)	None (MFG_18)	TRIAG(3,5,6)	Manufacture	
	Perform Clinical Testing (Clinical)	None (MFG_19)	TRIAG(5,8,9)	IDE	
REG	File for Investigational Approval from IRB (IA)	None (REG_1)	TRIAG(4,6,7)	Environment	
		WAIT	TRIAG(2,3,4)		
	Submit Investigational Device Exemption to FDA (IDE)	None (REG_2)	TRIAG(5,7,8)	IA	
		WAIT	TRIAG(4,5,6)		
	Submit for Premarket Notification (PMN)	None (REG_3)	TRIAG(3,4,5)	Clinical	
			TRIAG(8,9,10)		
	Prepare Insulin Pump For Market	None (PREPMARKET)	TRIAG(2,3,4)	PMN	
INSULIN PUMP READY FOR MARKET					

5.4 Determine Secondary Tasks

The Secondary Tasks were then determined and included in Table 6. Unlike the Primary Tasks, additional Secondary Tasks were added to Column 5.4 to accommodate the many components of the insulin pump as well as the complexity and uniqueness in the product and process development of the insulin pump. Like the Primary Tasks, the Secondary Tasks were also given unique labels for ease of future identification.

5.5 Estimate Duration of Tasks

Following the BOPP methodology, the estimated durations of Secondary Tasks and Primary Tasks without any Secondary Tasks were noted in Table 6. Due to time limitations, it was not possible to obtain historical data or expert opinions, from people who perform these tasks. Therefore, the task durations were estimated by the project planner for the purpose of this project. The estimated longest (X), most frequent (Y), and shortest (Z) possible durations for each of these tasks (in weeks) are presented in Column 5.5 in Table 6.

5.6 Determine Precedences between Primary Tasks

The precedences between the Primary Tasks were then determined, as shown in Column 5.6 in Table 6. Since the list of Primary Tasks was similar to the Primary Tasks in the general flowchart, the precedences were also similar. For example, for Primary Task, "Determine and Test Sterilization Method (Sterilization)", the predecessor is Primary Task, "Determine Production Assembly Process (Prod)." The Primary Task, "Determine and Test Sterilization Method (Sterilization)" is also the predecessor for three

subsequent Primary Tasks, "Determine Biocompatibility (Biocompatibility)", "Identify Storage Criteria (Storage)", and "Determine Packaging Material (Packaging)" that are performed simultaneously. The general precedences between Primary Tasks were confirmed through interviews and internet correspondence with experts on the subject of insulin pump process development and manufacturing.

5.7 Determine Precedences between Secondary Tasks

Due to the addition of Secondary Tasks to accommodate the insulin pump product and process development planning, additional precedences between the Secondary Tasks had to be determined. The method for determining the precedences between the Secondary Tasks was similar to the one used to determine the Primary Tasks. The precedences between the Secondary Tasks are entered in Column 5.7 in Table 6. For example, in order for Secondary Task, "Test Solenoid Motor (MFG_10)" to take place, the Secondary Task, "Assemble Solenoid Motor (MFG_9)" must be completed first.

5.8 Identify Potential Repeat Tasks

Potential Repeat Tasks were identified while developing the flowchart for the insulin pump product and process development, and are shown in the flowchart in Figure 40.

5.9 Develop Flowchart and Create Phantom Repeat Tasks

The insulin pump development and manufacturing was depicted in the form of a flowchart (Figure 40). Similar to the general biomedical device product and process

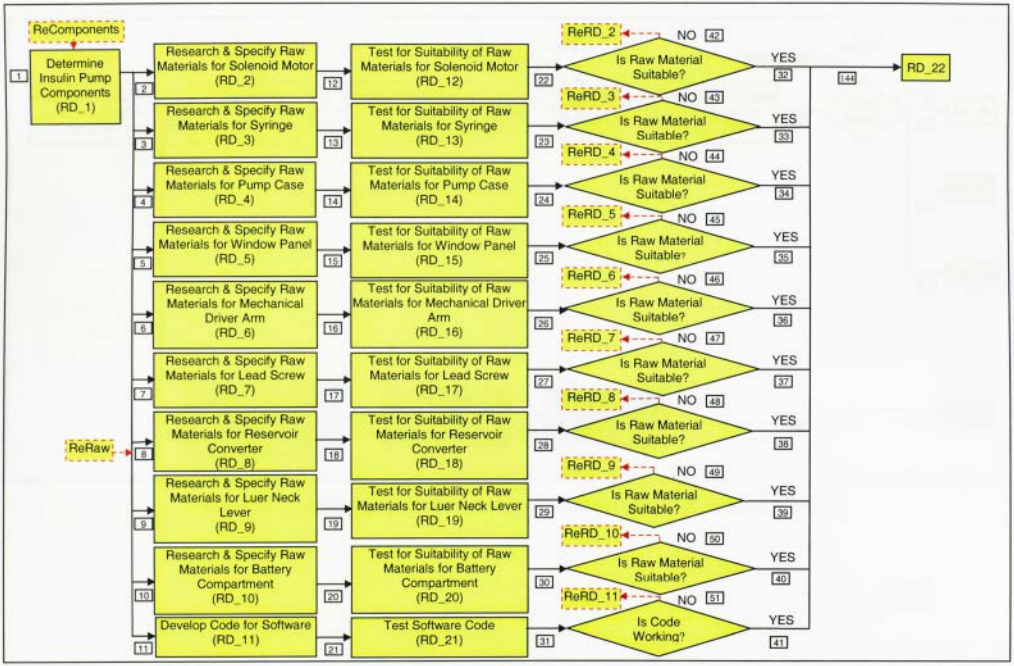

Figure 40: Insulin Pump Product and Process Development Flowchart.

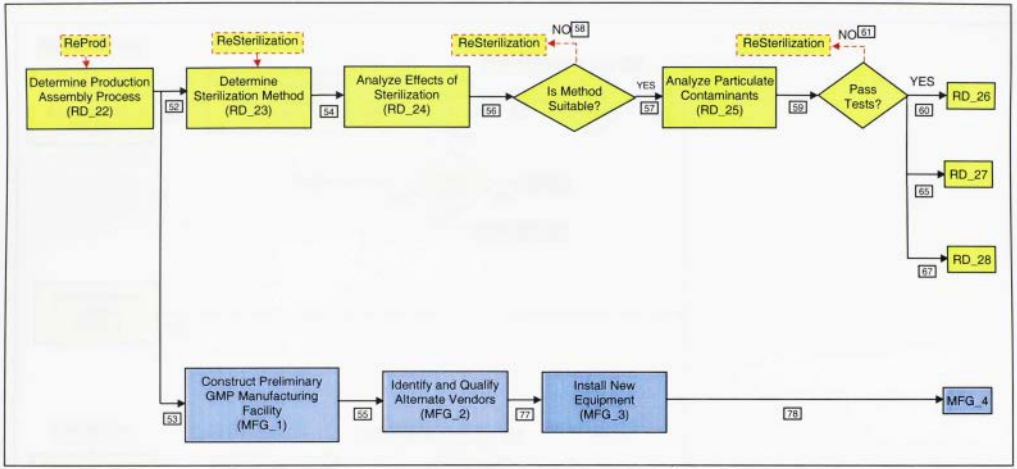

Figure 40: Insulin Pump Product and Process Development Flowchart (Cont.).

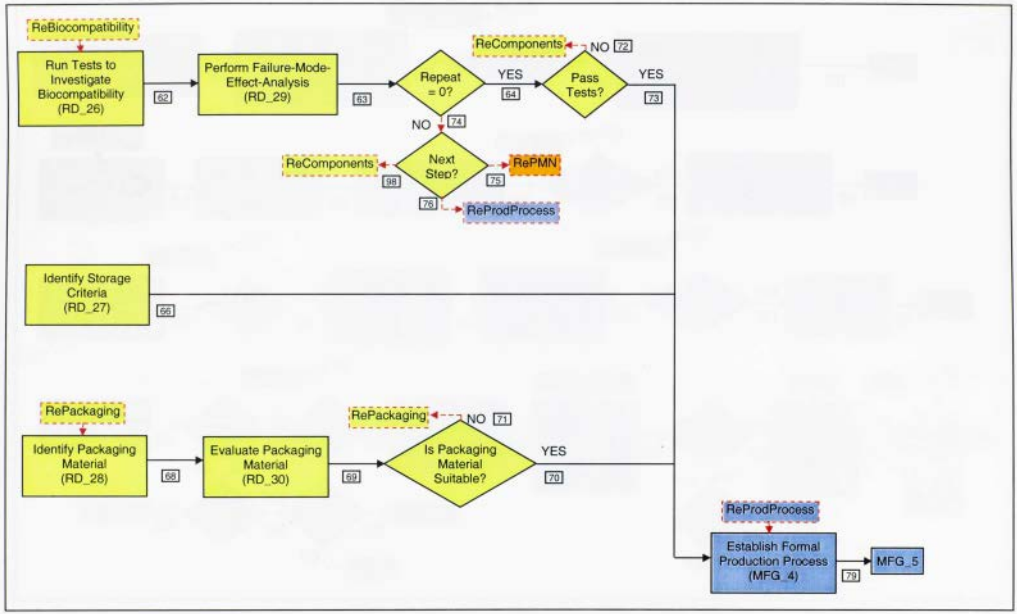

Figure 40: Insulin Pump Product and Process Development Flowchart (Cont.).

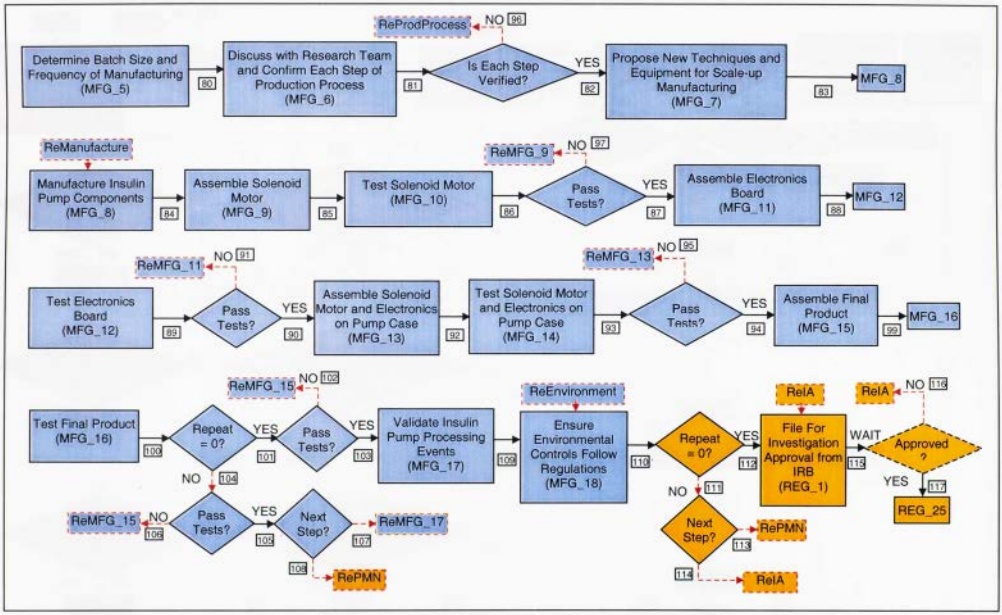

Figure 40: Insulin Pump Product and Process Development Flowchart (Cont.).

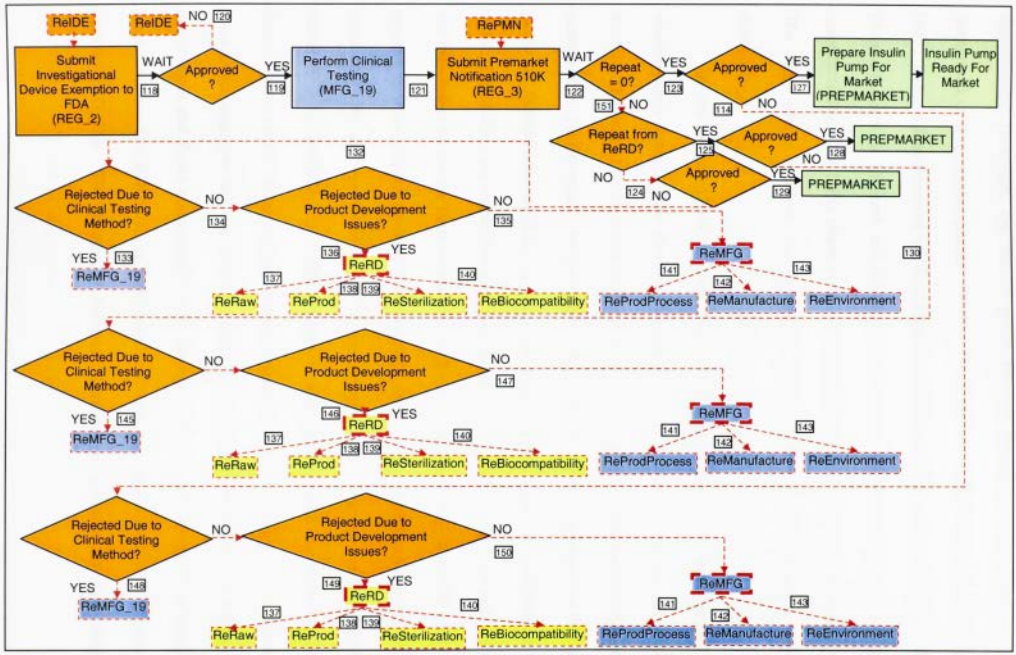

Figure 40: Insulin Pump Product and Process Development Flowchart (Cont.).

development flowchart, the insulin pump product and process development is also comprised of three major phases: Product Development or Research and Development (RD), Process Development or Manufacturing (MFG), and Regulatory (REG). The RD phase involves the research and development of raw materials and their preparation for manufacturing. The MFG phase is the actual manufacturing of the external insulin pump. The REG phase involves the handling of documents for the regulatory approval processes.

In this model, it was assumed that the RD stage begins after confirmation of an insulin pump design. The general biomedical device flowchart was the basis of this model. The project planner had to accommodate the specific components of the insulin pump within the flowchart. In the insulin pump RD phase, the components of the insulin pump are first determined (RD_1). Once this has been done, the raw materials for each of the components are researched and documented (RD_2 to RD_10). The raw materials are then tested to ensure their suitability for the insulin pump (RD_12 to RD_20). This process is iterated until suitable raw materials for each component are found. At the same time, the software code for the insulin pump "microcomputer" is developed and tested (RD_11 and RD_21). This process is also iterated until the software code is deemed satisfactory. Once the raw materials and the software codes are confirmed, the production assembly process is determined (RD_22). At this point, the MFG phase commences and flows concurrently with the RD phase in order to speed up design-to-market time. The RD phase is then continued with the determination of sterilization options (RD_23). The effects of different sterilization methods are then analyzed

(RD_24), and one selected. As shown in the flowchart, the process of finding the appropriate sterilization methods is also an iterative one.

After a sterilization method is determined, the method is analyzed for particulate contaminants (RD_25). If the level of particulate contaminants exceeds the level allowed by the FDA, a new sterilization method is determined. Otherwise, biocompatibility tests (RD_26), identification of storage criteria (RD_27), and identification of packaging materials (RD_28) are then performed concurrently. After biocompatibility tests are run, failure-mode-effect analysis is performed (RD_29). If discouraging results are produced by this analysis, the requirements for the insulin pump components need to be reanalyzed (RD_1). The packaging materials are also evaluated, and if found unsuitable, the identification of appropriate packaging materials is performed again.

The MFG phase is initialized with the construction of a preliminary Good Manufacturing Practice (GMP) manufacturing facility (MFG_1). Then, alternate vendors are identified and qualified to assure the highest quality of raw material is acquired (MFG_2). After that, new and more sophisticated equipment is added into this facility (MFG_3). A formal production process is then established (MFG_4). The batch size and frequency of manufacturing is determined (MFG_5). Each step of the production process is discussed with the research team to verify the process (MFG_6). If a problem is found within the proposed production process, an effort is made to revise the production process until it can be finalized and implemented. Otherwise, new techniques and equipment for scale-up manufacturing are proposed (MFG_7). All of the insulin pump components are then manufactured in batches (MFG_8). Next, the solenoid motor is assembled (MFG_9) and tested (MFG_10). This process is iterated until a high quality motor is manufactured.

The electronics board or microcomputer is then assembled (MFG_11) and tested (MFG_12). This is also an iterative process. The solenoid motor and electronics board are then assembled on the pump case (MFG_13) and tested (MFG_14). Then, all the components are assembled to form the final product (MFG_15) and tested (MFG_16). Once the final product passes all tests, the insulin pump processing events are validated to ensure consistent processing (MFG_17). Then, environmental controls are ensured to follow federal and state government regulations (MFG_18).

At this point, the REG process is begun. An Investigation Approval (IA) is filed and submitted to an Institutional Review Board or IRB (REG_1). This document is revised until it is approved by the IRB. Then, following approval, an Investigational Device Exemption (IDE) is submitted to the FDA (REG_2). This document is also revised until approved by the FDA. Clinical testing is then performed (MFG_19) and a Premarket Notification (PMN) is submitted to the FDA (REG_3). If not approved by the FDA, depending on the reasons given, the process could be repeated at Product Development (ReRD), Process Development (ReMFG), or at clinical testing (ReMFG_19), as depicted in the flowchart. For example, if problems are determined by the FDA to be in the Product Development phase (ReRD), there are probabilities that the problems are caused by the raw materials (ReRaw), the production assembly process (ReProd), the sterilization method (ReSterilization), or biocompatibility issues (ReBiocompatibility).

If problems are determined by the FDA to be in the Process Development phase (ReMFG), there are probabilities that the problems are within the production process (ReProdProcess), actual manufacturing (ReManufacture), or environmental controls

(ReEnvironment). After correcting the problems, the PMN is then resubmitted to the FDA. Upon final approval by the FDA, the insulin pump is ready to be manufactured in full-scale for the mass market (PREPMARKET).

As suggested in the BOPP methodology, each task is given a number to facilitate coordination with the simulation model that will be developed.

5.10 Estimate Probabilities of Potential Repeat Tasks and Phantom Repeat Tasks

The probabilities of potential Repeat Tasks and Phantom Repeat Tasks before and after PMN was submitted to the FDA, are then determined. In this example, little data was available concerning Repeat Tasks, while in an actual industry application, more information would be available. Therefore, due to the lack of actual historical data, these probabilities were estimated by the project planner. These probabilities are shown directly on the simulation network model.

5.11 Develop Simulation Network Model

Using the information gatheredin Steps 5.1 to 5.10, the simulation network model was developed using the various subnetworks suggested in the methodology. Again, the general biomedical device simulation network model provided the basis for the insulin pump model. The project planner had to include additional subnetworks to accommodate all the insulin pump components. An overview of the insulin pump simulation network is shown in Figure 41. Figure 42 shows an exploded version of the simulation network model. The project planner created this model using the student version of the AweSim 3.0 software, which only allowed the planner to use a maximum of 300 nodes and activities. Therefore, due to this constraint, the project planner had to make decisions on

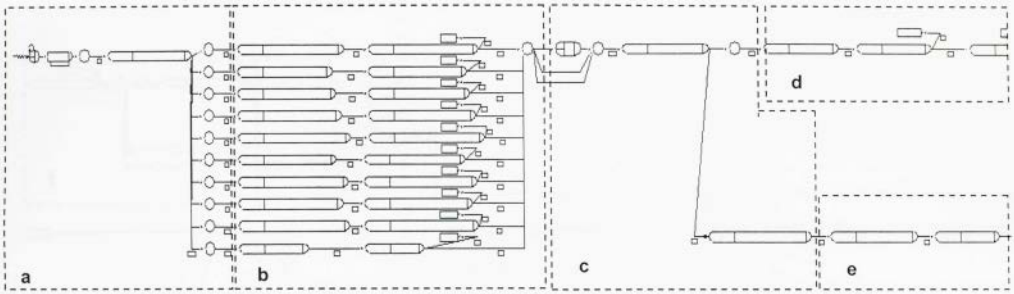

Figure 41: Simulation Network Model for Insulin Pump Product and Process Development - Overview.

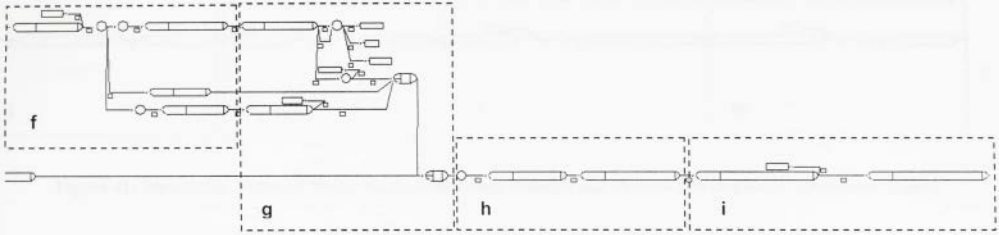

Figure 41: Simulation Network Model for Insulin Pump Product and Process Development - Overview (Cont.).

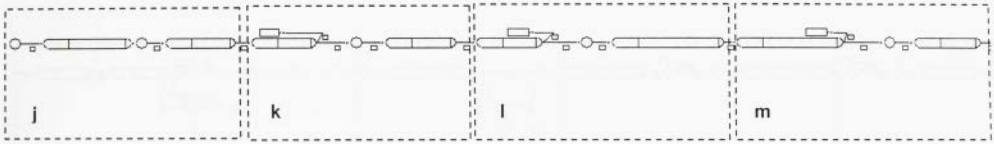

Figure 41: Simulation Network Model for Insulin Pump Product and Process Development - Overview (Cont.).

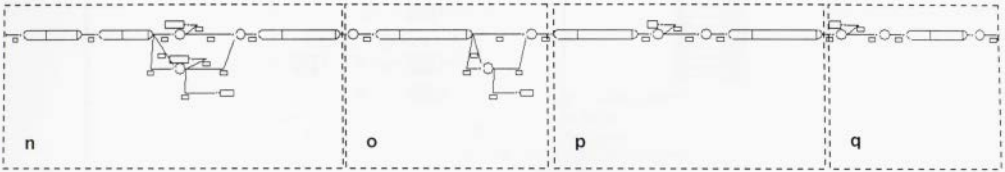

Figure 41: Simulation Network Model for Insulin Pump Product and Process Development - Overview (Cont.).

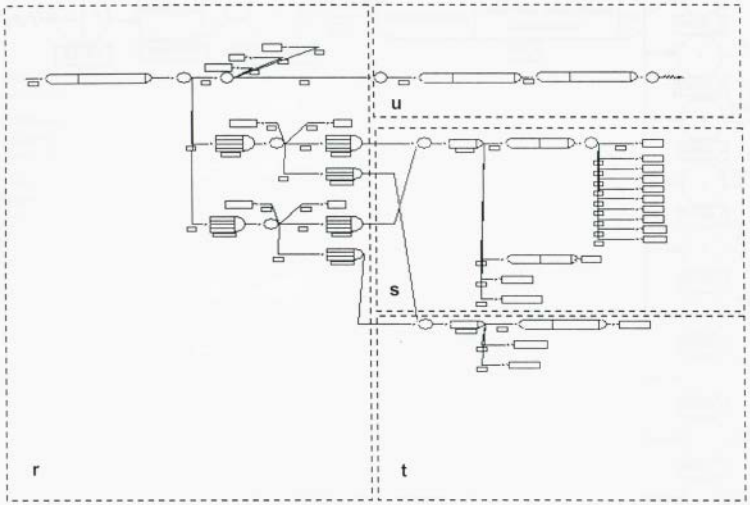

Figure 41: Simulation Network Model for Insulin Pump Product and Process Development - Overview (Cont.).

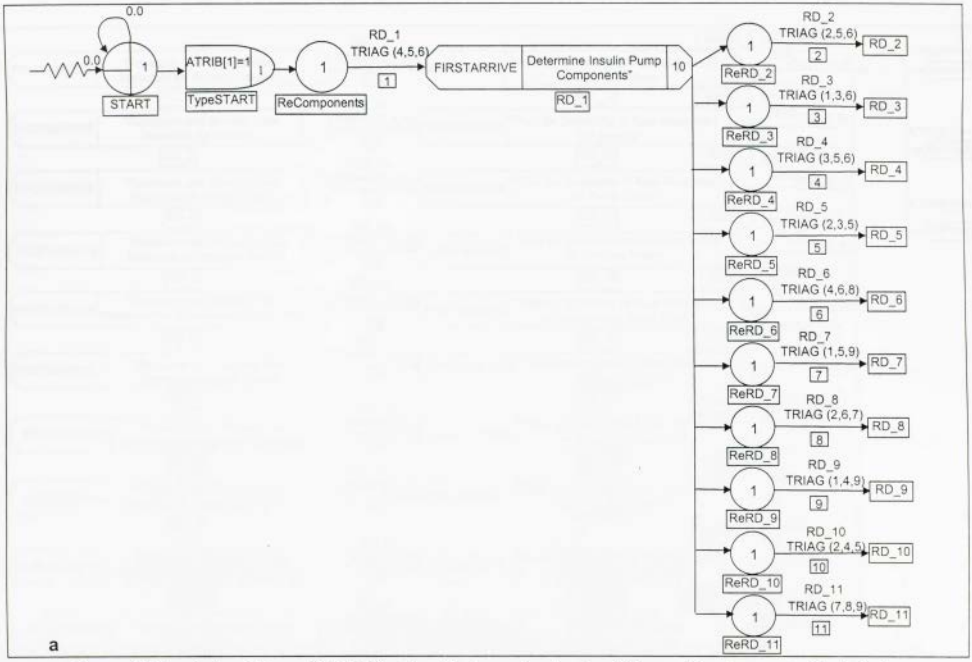

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded.

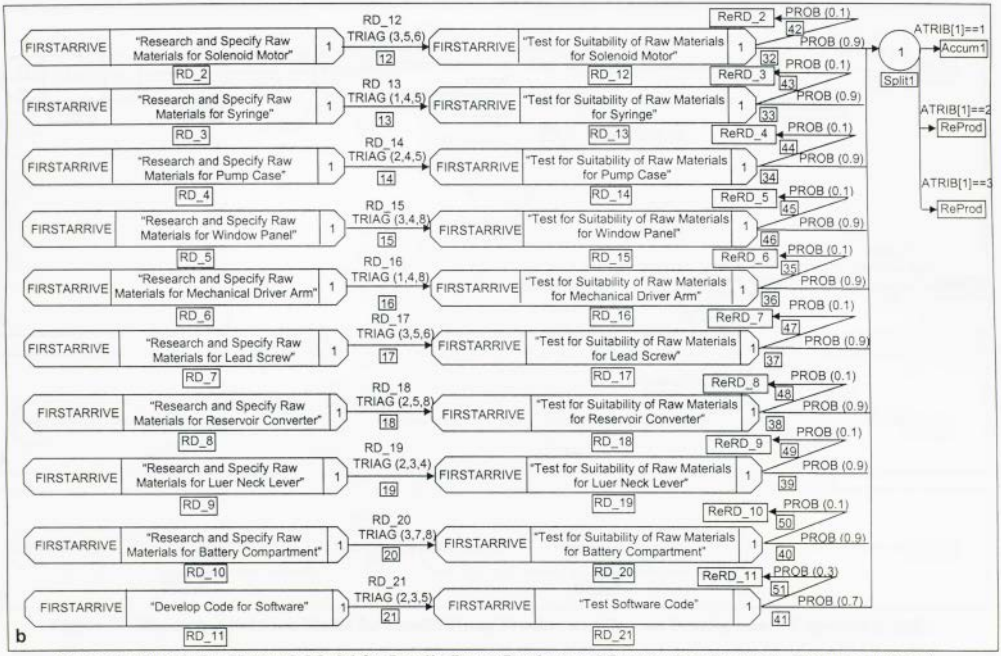

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

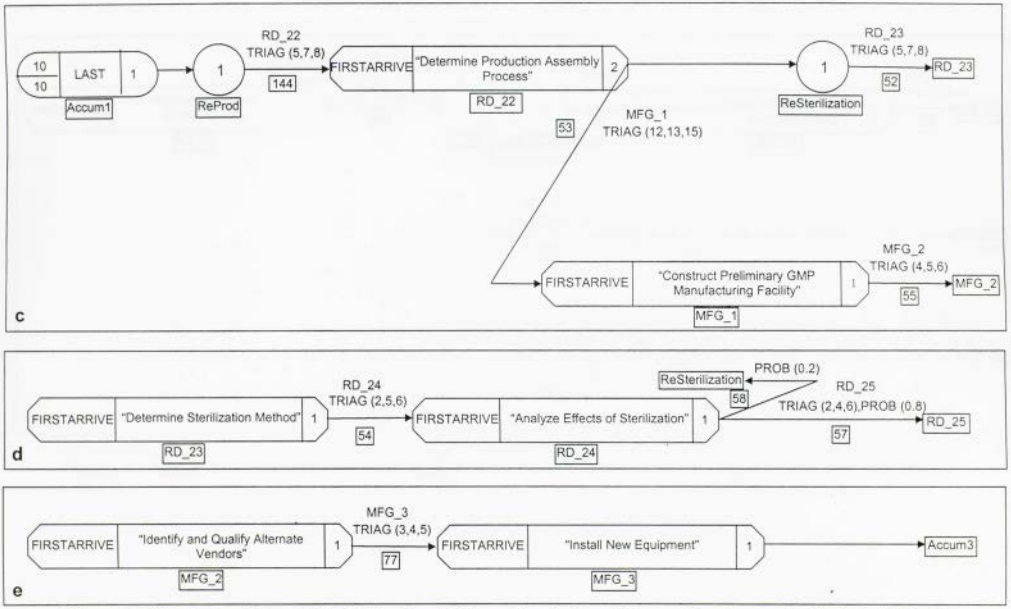

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

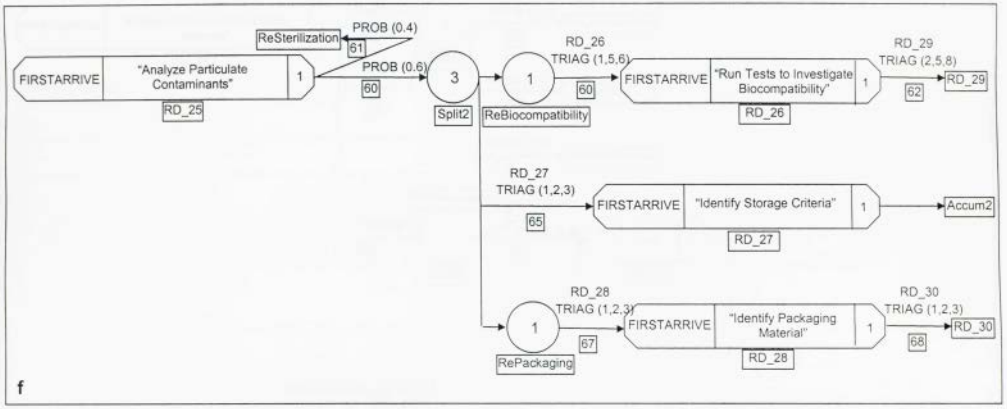

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

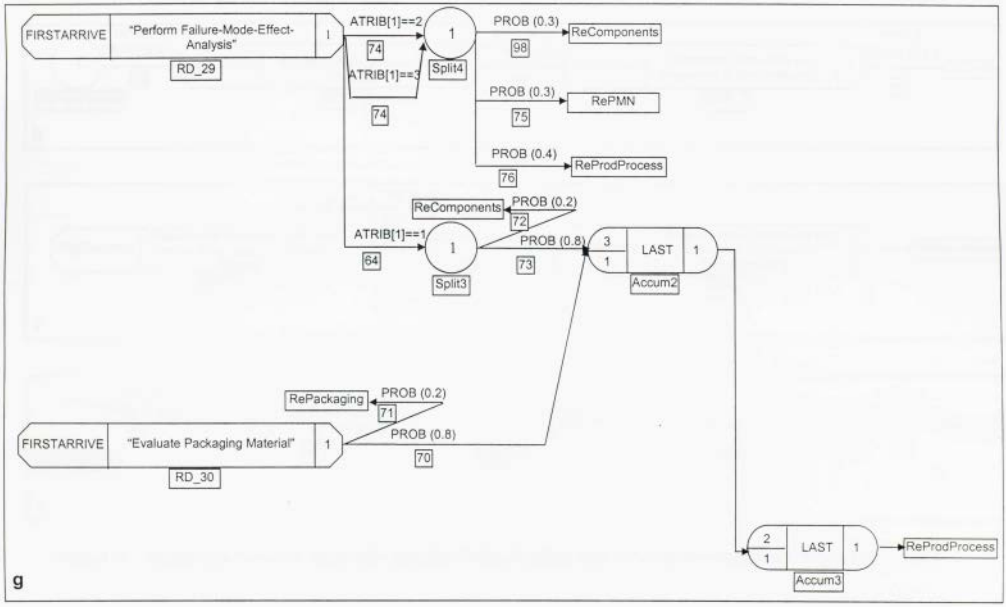

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

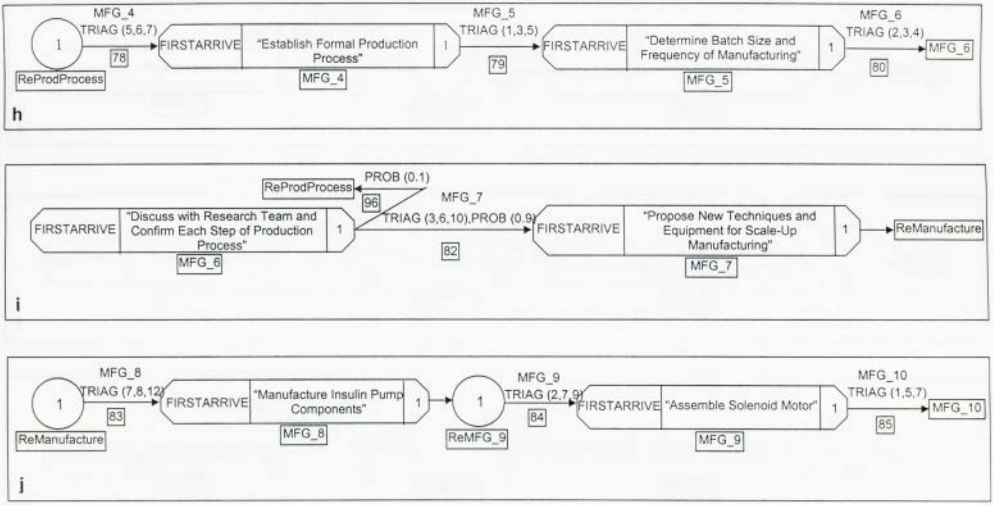

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

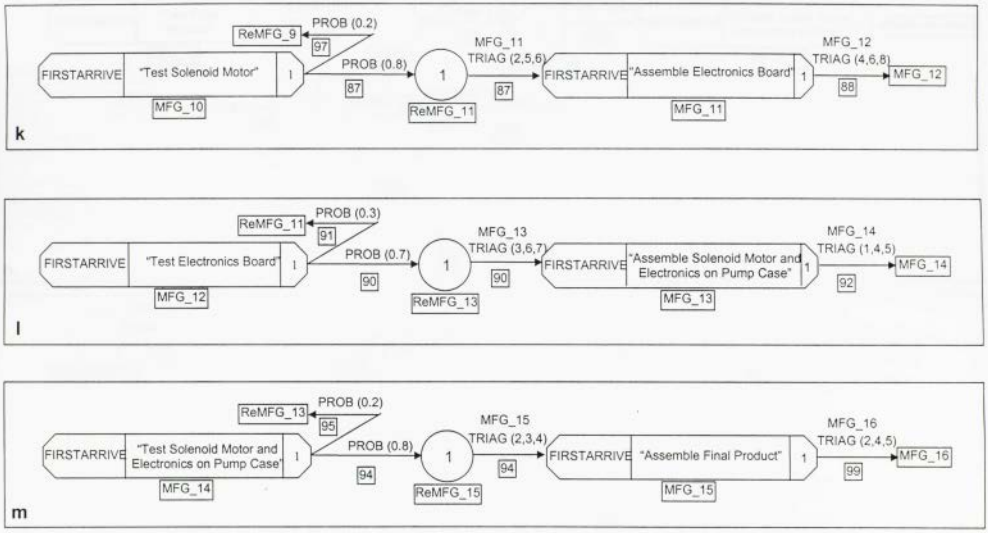

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

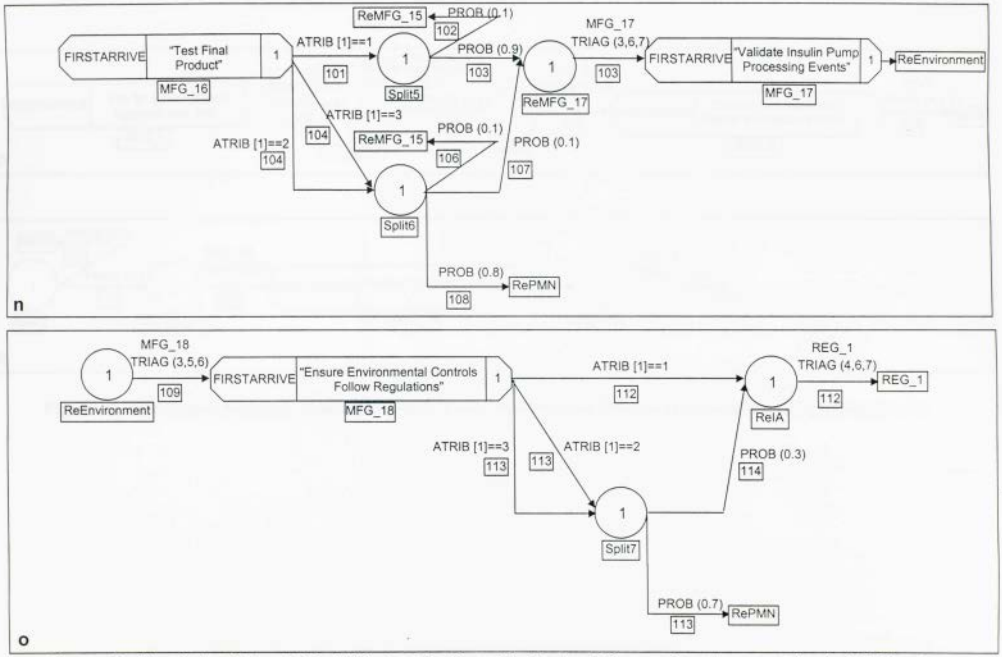

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

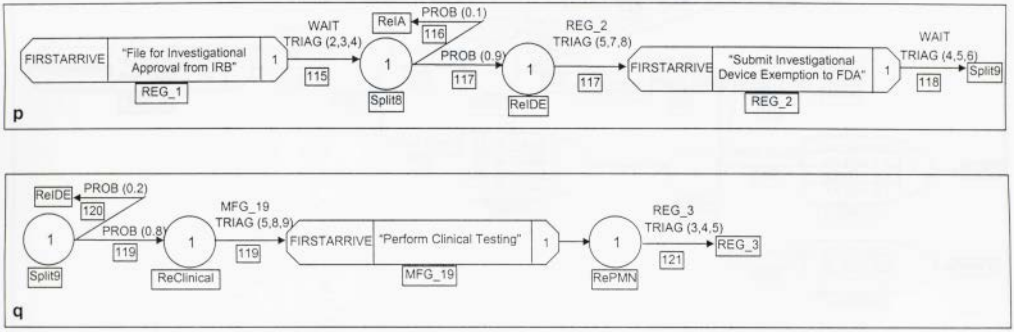

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

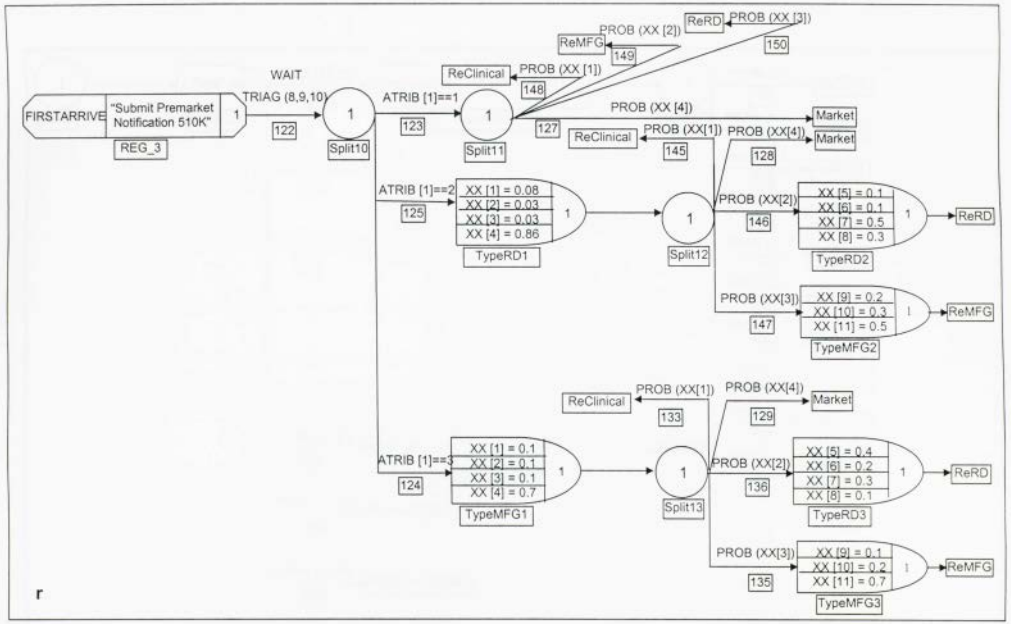

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

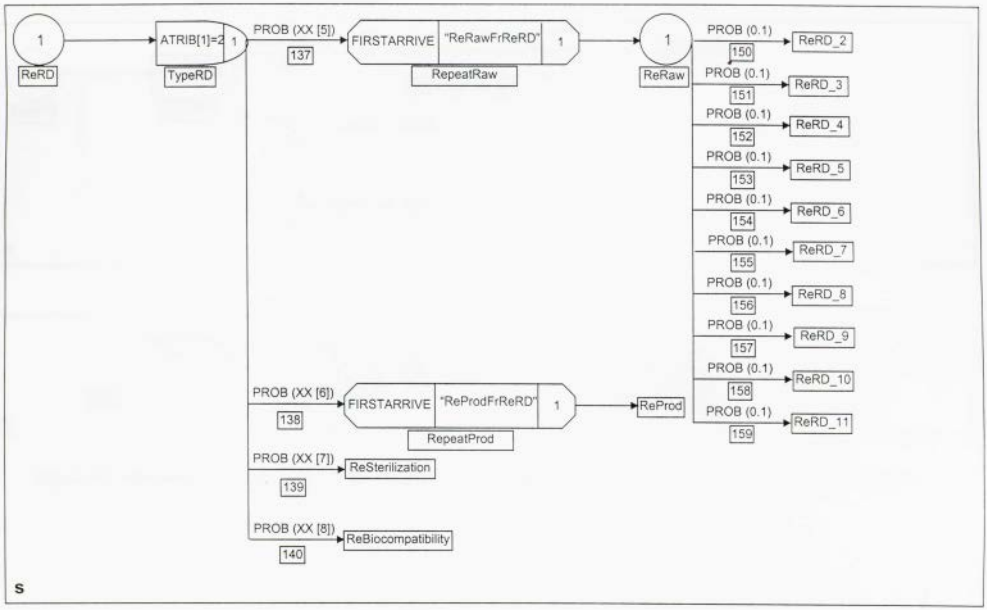

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

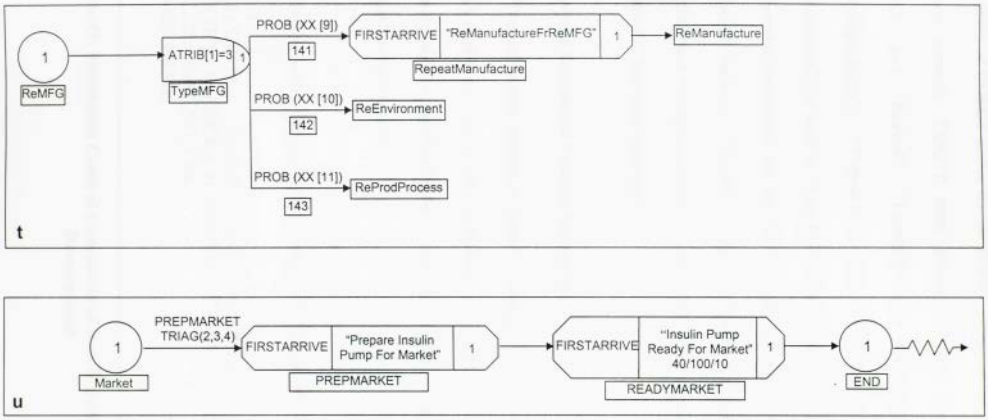

Figure 42: Simulation Network Model for Insulin Pump Product and Process Development - Exploded (Cont.).

the locations of COLCT nodes for the Repeat Tasks. In the general biomedical device simulation network, COLCT were placed between "Split5" and "ReMFG_11", "TypeRD" and "ReProd", "TypeRD" and "ReSterilization", "TypeRD" and "ReBiocompatibility", "TypeMFG" and "ReManufacture", "TypeMFG" and "ReEnvironment", as well as "TypeMFG" and "ReProdProcess". Due to the node and activity symbol limitations, for the insulin pump simulation network, COLCT nodes were only placed between "TypeRD" and "ReRaw", "TypeRD" and "ReProd", and "TypeMFG" and "ReManufacture". These locations were chosen arbitrarily to satisfy the 300 nodes and activities constraint.

5.12 Develop Simulation Control Statements

The developed simulation control statements for the insulin pump example are shown in Figure 43. In the GEN statement, the model was first simulated for 20 runs. After analyzing the results (Section 5.14), the number of runs was increased to 80 to obtain more accurate results.

```
GEN,"Dorene Seah","Insulin Pump Product and Process Development", 7/18/00, 20,
      YES,YES;
LIMITS,11,,,3;
INTLC,{{XX[1],0.1},{XX[2],0.3},{XX[3],0.4},{XX[4],0.2},{XX[5],0.2},{XX[6],0.3},
      {XX[7],0.1},{XX[8],0.4},{XX[9],0.1},{XX[10],0.6},{XX[11],0.3}};
INITIALIZE,0.0,800,NO,,YES;
NETWORK,READ;
FIN;
```

Figure 43: Simulation Control Statements of Insulin Pump Product and Process Development.

In the LIMITS statement, the maximum number of global variables, XX[] was 11 and the maximum number of attributes, ATRIB[] was 3.

In the INTLC statement, the variables, XX[1], XX[2], XX[3], and XX[4] represented initial probabilities of 0.1, 0.3, 0.4, and 0.2 of looping back in the simulation model from the submission of PMN (REG_3) to the clinical testing (ReMFG_19) task, the Manufacturing phase (ReMFG) and the Research and Development phase (ReRD), respectively. The variables, XX[5], XX[6], XX[7], and XX[8] represented the characteristics of an entity that was looped back to the "ReRD" phase (ATRIB[1]==2) and variables XX[9], XX[10], and XX[11] represented the characteristics of an entity that was looped back to the 'ReMFG" phase (ATRIB[1]==3). Therefore, the variables, XX[5], XX[6], XX[7], and XX[8], represented the initial probabilities of 0.2, 0.3, 0.1, and 0.2 of another loop back from the submission of PMN (REG_3) to the determination of raw materials (ReRaw), the determination of product assembly process (ReProd), determination of sterilization method and determination of biocompatibility. The variables, XX[9], XX[10], and XX[11] represented the initial probabilities of 0.1, 0.6, and 0.3 of another loop back from the submission of PMN (REG_3) to the manufacturing and assembling of biomedical device components (ReManufacture), determination of environmental controls (ReEnvironment), and determination of formal production process (ReProdProcess).

In the INITIALIZE statement, each run was set to be simulated for 800 weeks. As mentioned in the BOPP methodology, the NETWORK and FIN statements were left to their default values.

5.13 Run Simulation Model

After the development of the simulation network model and the associated control statements, the model was simulated.

5.14 Analyze Results

As shown in Figure 44, when the model was simulated for 20 runs of 80 weeks each, the results indicated that the insulin pump would be ready for market within a mean time of 256.4 weeks. The standard deviation was 58.3 weeks. Therefore, the half-width of the 95% confidence interval was:

$$\begin{aligned} h_0 &= t_{n_0-1,1-\alpha/2}\frac{s}{\sqrt{n_0}} \\ &= 2.09\frac{(58.3)}{\sqrt{20}} \\ &= 27.3 \end{aligned}$$

The half-width represents some 10.64% error in the point estimate of 256.4. Reducing this error would make the results more accurate. For example, the project planner decided to reduce this error by half. Therefore, using the formula suggested in the methodology to determine the number of runs needed to reduce to a known half-width, h of 13.6:

$$\begin{aligned} n &\approx n_0 \cdot \frac{h_0^2}{h^2} \\ &\approx 20\frac{(27.3)^2}{(13.6)^2} \\ &\approx 80 \; runs \end{aligned}$$

Therefore, the model was then simulated for 80 runs. The results for the 80th run are shown in Figure 45. Compared to the original error of 10.64%, the error has been

reduced to 5.32% within the point estimate of 274.1. The output echo and intermediate reports for the simulation are shown in Appendices A and B.

** AweSim SUMMARY REPORT **
Sun Mar 18 21:55:05 2001
Simulation Project : Insulin Pump Product and Process Development
Modeler : Dorene Seah
Date : 7/18/00
Scenario : BASECASE

Run number 20 of 20
Current simulation time : 274.337955
Statistics cleared at time : 0.000000

** OBSERVED STATISTICS REPORT for scenario BASECASE **

Label	Mean Value	Standard Deviation	No. of Obs.	Min. Value	Max. Value
Determine Insulin Pump Components	5.011	0.401	23	4.199	5.861
Research and Specify Raw Materials for Solenoid Motor	9.525	0.809	27	7.964	11.301
Research and Specify Raw Materials for Syringe	7.992	1.062	28	6.843	10.489
Research and Specify Raw Materials for Pump Case	9.380	0.805	29	8.43	11.017
Research and Specify Raw Materials for Window Panel	8.483	0.849	26	7.254	9.889
Research and Specify Raw Materials for Mechanical Driver Arm	11.037	0.910	26	9.670	12.641
Research and Specify Raw Materials for Lead Screw	9.239	1.390	25	6.948	12.908
Research and Specify Raw Materials for Reservoir Converter	10.321	1.300	25	7.198	12.410
Research and Specify Raw Materials for Luer Neck Lever	9.745	1.922	28	6.796	13.691
Research and Specify Raw Materials for Battery Compartment	8.717	0.553	28	7.486	9.761
Develop Code for Software	13.050	0.729	24	12.045	14.313
Test for Suitability of Raw Materials for Solenoid Motor	14.264	0.871	27	12.372	16.106

Figure 44: Results of 20th Simulation Run – Observed Statistics Report.

Label	Mean Value	Standard Deviation	No. of Obs.	Min. Value	Max. Value
Test for Suitability of Raw Materials for Syringe	11.647	1.317	28	9.759	15.133
Test for Suitability of Raw Materials for Pump Case	13.024	1.080	29	11.503	15.347
Test for Suitability of Raw Materials for Window Panel	13.916	1.431	26	11.339	15.753
Test for Suitability of Raw Materials for Mechanical Driver Arm	15.229	1.949	26	12.233	19.583
Test for Suitability of Raw Materials for Lead Screw	13.806	1.625	25	11.559	17.714
Test for Suitability of Raw Materials for Reservoir Converter	15.583	1.915	25	11.773	19.295
Test for Suitability of Raw Materials for Luer Neck Lever	12.741	1.851	28	9.609	16.753
Test for Suitability of Raw Materials for Battery Compartment	14.625	1.147	28	12.962	16.259
Test Software Code	16.496	1.119	24	14.798	18.98
Determine Production Assembly Process	29.113	5.425	27	22.456	41.624
Determine Sterilization Method	36.498	5.627	44	29.226	49.292
Analyze Effects of Sterilization	40.863	5.51	44	33.995	52.703
Analyze Particulate Contaminants	45.810	5.906	40	37.625	59.064
Run Tests to Investigate Biocompatibility	58.632	14.945	27	40.539	81.361
Perform Failure-Mode-Effect-Analysis	63.268	14.821	27	44.878	86.388
Identify Storage Criteria	56.477	14.866	26	39.496	79.493
Identify Packaging Material	55.715	14.749	29	40.258	79.880
Evaluate Packaging Material	57.676	14.772	29	42.148	81.523
Construct Preliminary GMP Manufacturing Facility	42.153	5.336	26	36.056	54.674

Figure 44: Results of 20th Simulation Run – Observed Statistics Report (Cont.).

Label	Mean Value	Standard Deviation	No. of Obs.	Min. Value	Max. Value
Identify and Qualify Alternate Vendors	47.261	5.359	26	41.414	59.632
Install New Equipment	51.161	5.456	26	44.79	63.955
Establish Formal Production Process	88.663	30.466	48	51.420	157.100
Determine Batch Size and Frequency of Manufacturing	90.963	30.553	47	54.415	160.029
Discuss with Research Team and Confirm Each Step of Production Process	93.969	30.620	47	57.440	163.150
Propose New Techniques and Equipment for Scale-Up Manufacturing	100.656	30.236	44	66.086	167.339
Manufacture Insulin Pump Components	109.370	30.875	43	75.225	175.751
Assemble Solenoid Motor	116.166	31.220	53	81.070	180.803
Test Solenoid Motor	121.113	31.602	52	86.261	186.513
Assemble Electronics Board	124.193	29.083	66	90.059	190.734
Test Electronics Board	130.166	28.936	66	96.257	195.550
Assemble Solenoid Motor and Electronics Board on Pump Case	143.810	31.961	54	101.658	212.444
Test Solenoid Motor and Electronics Board on Pump Case	146.316	32.233	53	103.843	215.225
Assemble Final Product	153.070	29.695	45	109.432	217.931
Test Final Product	156.614	29.985	45	112.661	222.098
Validate Insulin Pump Processing Events	166.589	30.442	32	119.334	226.996
Ensure Environmental Controls Follow Regulations	167.944	32.316	38	123.549	231.327
File For Investigational Approval by IRB	178.206	31.980	35	128.847	236.423

Figure 44: Results of 20th Simulation Run – Observed Statistics Report (Cont.).

Label	Mean Value	Standard Deviation	No. of Obs.	Min. Value	Max. Value
Submit Investigational Device Exemption to FDA	184.625	32.497	37	138.779	247.463
Perform Clinical Testing	197.754	30.400	32	149.600	259.653
Submit Premarket Notification 510K	195.805	27.349	45	154.087	263.659
Prepare Insulin Pump for Market	256.364	58.335	20	180.183	386.383
Insulin Pump Ready for Market	**256.364**	**58.335**	**20**	**180.183**	**386.383**
ReRawFrReRD	253.336	89.812	2	189.829	316.842
ReProdFrReRD	265.236	37.383	2	238.802	291.670
ReManufactureFrReMFG	198.608	0.000	1	198.608	198.608

Figure 44: Results of 20th Simulation Run – Observed Statistics Report (Cont.).

** AweSim SUMMARY REPORT **
Sun Mar 18 21:55:05 2001
Simulation Project : Insulin Pump Product and Process Development
Modeler : Dorene Seah
Date : 7/18/00
Scenario : BASECASE

Run number 20 of 20
Current simulation time : 274.337955
Statistics cleared at time : 0.000000

** OBSERVED STATISTICS REPORT for scenario BASECASE **

Label	Mean Value	Standard Deviation	No. of Obs.	Min. Value	Max. Value
Determine Insulin Pump Components	5.004	0.380	112	4.199	5.931
Research and Specify Raw Materials for Solenoid Motor	9.479	0.856	126	6.719	11.351
Research and Specify Raw Materials for Syringe	8.273	0.940	127	5.946	11.014
Research and Specify Raw Materials for Pump Case	9.619	0.736	124	8.240	11.205
Research and Specify Raw Materials for Window Panel	8.388	0.697	130	6.589	9.921
Research and Specify Raw Materials for Mechanical Driver Arm	11.080	0.861	130	9.233	13.158
Research and Specify Raw Materials for Lead Screw	9.335	1.818	122	6.154	13.496
Research and Specify Raw Materials for Reservoir Converter	10.162	1.075	122	7.198	12.410
Research and Specify Raw Materials for Luer Neck Lever	9.681	1.840	125	6.174	14.107
Research and Specify Raw Materials for Battery Compartment	8.759	0.638	125	7.241	10.513
Develop Code for Software	13.054	0.688	122	12.045	14.421
Test for Suitability of Raw Materials for Solenoid Motor	13.992	0.976	123	11.110	16.106
Test for Suitability of Raw Materials for Syringe	11.598	1.179	126	9.280	15.133
Test for Suitability of Raw Materials for Pump Case	13.379	0.962	120	11.426	15.481

Figure 45: Results of 80th Simulation Run – Observed Statistics Report.

Label	Mean Value	Standard Deviation	No. of Obs.	Min. Value	Max. Value
Test for Suitability of Raw Materials for Window Panel	13.333	1.352	128	10.705	16.289
Test for Suitability of Raw Materials for Mechanical Driver Arm	15.045	1.855	127	11.592	19.583
Test for Suitability of Raw Materials for Lead Screw	14.064	1.962	119	10.849	18.188
Test for Suitability of Raw Materials for Reservoir Converter	15.297	1.669	117	11.63	19.295
Test for Suitability of Raw Materials for Luer Neck Lever	12.710	1.792	123	8.819	16.978
Test for Suitability of Raw Materials for Battery Compartment	14.866	1.402	122	11.600	17.435
Test Software Code	16.526	0.923	118	14.713	18.980
Determine Production Assembly Process	29.634	4.481	262	21.169	45.042
Determine Sterilization Method	36.486	4.708	414	26.856	51.638
Analyze Effects of Sterilization	40.802	5.126	382	31.420	56.986
Analyze Particulate Contaminants	45.499	5.619	295	35.124	63.465
Run Tests to Investigate Biocompatibility	68.556	19.865	174	39.675	112.303
Perform Failure-Mode-Effect-Analysis	73.489	20.215	168	42.138	119.604
Identify Storage Criteria	66.587	19.648	165	36.963	109.715
Identify Packaging Material	67.249	20.231	204	37.203	110.639
Evaluate Packaging Material	68.799	19.866	201	39.109	112.403
Construct Preliminary GMP Manufacturing Facility	43.065	4.698	192	34.499	59.214
Identify and Qualify Alternate Vendors	47.984	4.860	181	39.188	64.340

Figure 45: Results of 80th Simulation Run – Observed Statistics Report (Cont.).

Label	Mean Value	Standard Deviation	No. of Obs.	Min. Value	Max. Value
Install New Equipment	52.025	4.901	180	42.955	69.189
Establish Formal Production Process	85.233	24.818	422	51.420	157.100
Determine Batch Size and Frequency of Manufacturing	87.785	24.431	401	54.415	160.029
Discuss with Research Team and Confirm Each Step of Production Process	90.963	24.291	385	57.44	163.150
Propose New Techniques and Equipment for Scale-Up Manufacturing	98.035	25.150	298	63.442	168.908
Manufacture Insulin Pump Components	106.322	26.518	240	72.013	176.378
Assemble Solenoid Motor	112.933	28.454	259	77.271	182.328
Test Solenoid Motor	117.596	29.386	240	80.213	186.513
Assemble Electronics Board	121.949	28.936	278	84.785	197.598
Test Electronics Board	127.696	28.785	273	90.732	202.952
Assemble Solenoid Motor and Electronics Board on Pump Case	142.723	30.146	232	95.552	212.444
Test Solenoid Motor and Electronics Board on Pump Case	146.126	30.343	226	99.689	215.225
Assemble Final Product	152.193	29.652	195	102.241	217.931
Test Final Product	156.057	29.829	191	106.243	222.098
Validate Insulin Pump Processing Events	165.767	32.239	112	111.810	231.015
Ensure Environmental Controls Follow Regulations	168.010	32.519	132	116.704	236.636
File For Investigational Approval by IRB	178.181	33.447	120	122.015	242.764
Submit Investigational Device Exemption to FDA	186.699	33.441	134	132.696	251.446

Figure 45: Results of 80th Simulation Run – Observed Statistics Report (Cont.).

Label	Mean Value	Standard Deviation	No. of Obs.	Min. Value	Max. Value
Perform Clinical Testing	199.332	31.071	116	144.052	271.071
Submit Premarket Notification 510K	198.392	27.525	196	148.001	275.700
Prepare Insulin Pump for Market	274.100	61.806	80	160.024	405.375
Insulin Pump Ready for Market	**274.100**	**61.806**	**80**	**160.024**	**405.375**
ReRawFrReRD	224.359	48.994	7	170.891	316.842
ReProdFrReRD	248.338	38.206	8	195.635	291.670
ReManufactureFrReMFG	191.064	10.669	2	183.520	198.608

Figure 45: Results of 80th Simulation Run – Observed Statistics Report (Cont.).

Figure 45 shows that the mean completion time for the insulin pump project was estimated at 274.1 weeks. The shortest possible completion time of product and process development of the insulin pump was an estimated 160.0 weeks. The longest possible completion time was estimated at 405.4 weeks. The standard deviation was 61.8 weeks. Therefore, the standard error of the mean project completion times is approximately 6.9 weeks. Assuming a normal distribution, a 95% confidence interval for the mean project completion is approximately two standard errors from the mean (Pritsker et al., 1994). Therefore, it can be estimated that there is a probability of 0.95 that the true mean of the project's completion time lies between 260.3 and 287.9 weeks.

A histogram report of the results is shown in Figure 46. By analyzing the histogram report (Figure 46), it is possible to estimate the probability of the project being completed in a specified duration. For example, by looking at the 13th cell of the histogram report, it can be seen that there were 6 cases, or observed runs, where the

insulin pump product and process development completion time were greater than 210 weeks but less than or equal to 220 weeks.

Observed Frequency	Relative Frequency	Cumulative Frequency	Upper Cell Limit
0	0.000	0.000	100
0	0.000	0.000	110
0	0.000	0.000	120
0	0.000	0.000	130
0	0.000	0.000	140
0	0.000	0.000	150
0	0.000	0.000	160
1	0.013	0.013	170
0	0.000	0.013	180
3	0.037	0.050	190
3	0.037	0.087	200
9	0.113	0.200	210
6	0.075	0.275	220
5	0.063	0.338	230
3	0.037	0.375	240
3	0.037	0.412	250
3	0.037	0.45	260
3	0.037	0.487	270
3	0.037	0.525	280
6	0.075	0.600	290
4	0.050	0.650	300
5	0.063	0.713	310
3	0.037	0.750	320
3	0.037	0.787	330
3	0.037	0.825	340
5	0.063	0.887	350
3	0.037	0.925	360
0	0.000	0.925	370
0	0.000	0.925	380
3	0.037	0.963	390
1	0.013	0.975	400
2	0.025	1.000	410
0	0.000	1.000	420
0	0.000	1.000	430
0	0.000	1.000	440
0	0.000	1.000	450
0	0.000	1.000	460
0	0.000	1.000	470
0	0.000	1.000	480
0	0.000	1.000	490
0	0.000	1.000	500
0	0.000	1.000	INFINITY

Figure 46: Observed Statistics Histogram Report for 80th Run.

The relative frequency of this observation is 7.5%.The cumulative frequency associated with 220 weeks is 0.28. Therefore, it can be estimated that the probability of the project being completed within 220 weeks is 0.28. The estimated probability of the project taking longer than 220 weeks is 0.72. A graphical version of the histogram report is shown in Figure 47.

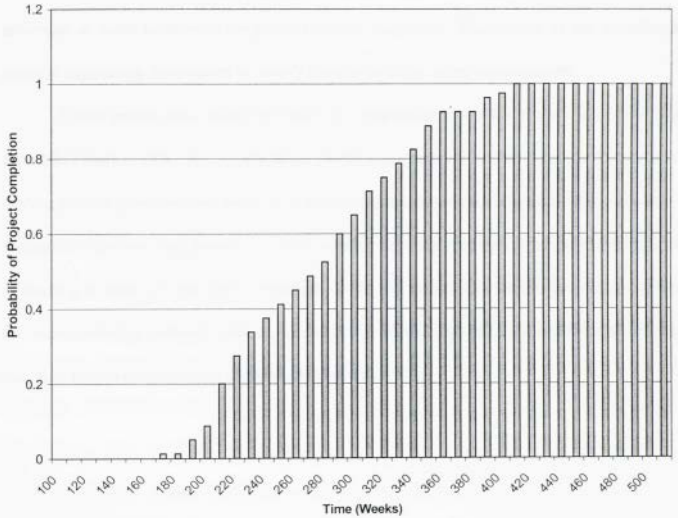

Figure 47: Cumulative Frequency of Project Completion Times for 80 Runs.

These simulation results also provide a strong basis for predicting two of the main performance measures of project planning: the project completion time and the risks involved with the project. Based on these results, biomanufacturing companies are able

to make product and process decisions. By doing so, they are also able to make better investment decisions.

Based on the estimated duration of the entire biomedical device product and process development provided by the results of the simulation, project planners may choose to add or delete tasks deemed necessary for the project and to reduce or add more time to the project. The project planner may also choose to review the precedences of activities in order to shorten the project completion time. The results of the simulation provide supporting documents to justify these actions to upper management.

These results also show the risks of completing a certain project later than the scheduled market date. If the simulation shows high probability that a certain biomedical device project plan will not meet its scheduled date, upper management may choose to change the timeline and propose a more feasible date for marketing the product, instead of striving to meet an impossible schedule. This will satisfy two important criteria within the manufacturing industry, that is, to deliver products that are high quality and on the date that they were promised (on-time deliveries).

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

This chapter provides the summary and conclusions of this research as well as recommendations for future research.

6.1 Summary

The rapidly changing biomedical device industry and the associated pace of the advancement of technology requires that biomedical device companies release products into the marketplace as fast as possible to recoup the investment made into them as well as to deal with fierce competition. The product and process development of biomedical devices differ greatly from other products due to the uniqueness of biomanufacturing. The field of biomanufacturing is unique in terms of the integration of advanced technologies, the integration of biomedical devices with the human body, government regulations, biomedical product liability issues, social and ethical issues, and sterilization methods. Although well-planned product and process development can ensure rapid time to market, fast production ramp-up, and more solid proprietary position for biomanufacturers, most biomedical device manufacturers have the tendency to concentrate on improving product development issues rather than accelerating their process development.

There are many methods recommended to accelerate product development. They include implementation of support systems and techniques, speeding up activities or tasks, reduction of parts or components in products, supplier involvement, simplifying operations, eliminating delays, eliminating steps, and processing steps in parallel. These

methods can be incorporated into a simulation network model during the project planning stage to estimate their effectiveness, while taking the uniqueness of biomanufacturing under consideration.

The methodology for developing the general biomedical device product and process development simulation model consists of 14 steps from the development of the model to the analysis of the results. For ease of use, a template for this simulation model has been provided. A project planner will be able to save time by modifying the template to meet the needs of a specific biomedical device. Otherwise, a unique biomedical device product and process development simulation network model can be developed by following the instructions in the methodology.

6.2 Conclusions

The objective of developing a simulation tool using the SLAM II language to facilitate project management in biomedical device product and process development was accomplished. Through extensive research, taking the uniqueness of biomanufacturing into consideration, a methodology was developed that addresses the needs of biomedical device companies in improving the planning related to the development of their products and associated production processes. This research concentrated on the creation of a simulation tool that considers product and process development failures and the reengineering of those activities, the impact of government regulations and the approval process, along with their impact on product and process development, as well as multiple subprocess failures with time variant probabilities. This was achieved through the development of a methodology to aid the project planner in developing and using a simulation network model for biomedical device product and process development. This

research also provided an example application of the methodology depicting the product and process development of an external insulin pump.

6.3 Recommendations for Future Research

Besides project completion time and the associated risks of the project being completed within a certain duration, another key measure in project management and planning is project costs. Therefore, for future research, it would be beneficial to expand the simulation model to include project costs. The SLAM II language can be used to incorporate this performance measure into a simulation model.

Due to the limitations of time and information availability, the durations of all tasks and probabilities of Repeat Tasks were estimated by the project planner. In actual industry application, these durations and probabilities should be constantly validated, monitored, and updated during and after the actual project. The durations can be obtained through discussions with the personnel who have experience in performing the tasks and planning documents such as work center reports that include standard labor run rates. These durations can be validated by comparing the estimated durations with the durations in actual labor reports. Project completion time can also be validated by comparing the simulation estimated time that the biomedical device will be ready for market with the actual time the biomedical device is ready for market. These data will be helpful in future creation of more accurate project planning models.

The biomedical device project planning model that was created within this thesis concentrated on product and process development tasks. On a broader perspective, the BOPP methodology can also be used to incorporate other groups within an organization,

such as marketing and finance, in the development process. This may result in a more accurate planning as all the departments are involved in the planning process.

It is also recommended that research is made to investigate the linking of popular project planning software such as Microsoft Project with SLAM II, in order to increase usability. Most project planning software in the market do not have the capability of estimating risks or probabilities of project failure. The integration of these software and the simulation in the BOPP methodology will greatly benefit project planners.

It would also be helpful if an object-oriented interface is created for the project planner to enter the information needed to develop the flowchart and simulation model. This interface should include Primary and Secondary task names, durations, and precedences. Not only will this ease understanding of the required inputs, it will also make it easier to track data inputs. If the interface is linked to a database, it will also enable the project planner to track historical data, as the database can be updated for accuracy during the project itself.

It is also possible to build a model generator, which will automatically create the simulation model, based on data in the templates. This addition would greatly enhance the usability of the BOPP methodology and make it available to a wider audience. The user interface could also be enhanced to run the models automatically, and collect and display data in forms that support the project planner.

REFERENCES

Abernathy, W.J. & Utterback, J.M. (1978). Patterns of industrial innovation. *Technology Review*, 80(7), 2-9.

Albert, D.E. & Wallin, R.F. (February 1998). A practical guide to ISO 10993-14: Materials characterization. *Medical Device and Diagnostic Industry*, *20*(2), 96-99.

Badiru, A. (1991a). STARC 2.0: An improved PERT network simulation tool. In *Proceedings of the 13th Annual Conference on Computers and Industrial Engineering*, *20*(3), 389-400.

Badiru, A. (1991b). A simulation approach to PERT network analysis. *Simulation*, *57*(4), 245-255.

Badiru, A. B. (1996). *Project management in manufacturing and high technology Operations*. (2nd ed.). New York, NY: John Wiley & Sons, Inc.

Bergen, S.A. (1986). *Project management: An introduction to issues in industrial research and development*. Basil Blackwell Ltd.

Biotechnology (April 1999). U.S. Patent and Trademark Office. *Technology Profile Report*. Patent Examining Technology Center, Groups 1630-1650, 1/1977 - 1/1998.

Bok, S.H., Bhattacharjee, A., Nee, A.Y.C., Pho, R.W.H., Teoh, S.H., & Lim, S.Y.E. (1990). Computer-aided design and computer-aided manufacture (CAD-CAM) applications in cosmetic below-elbow prostheses. *Annals Academy of Medicine*, *19*(5), 699-705.

Chatfield, C.S. & Johnson, T.D. (2000). *Step by step: Microsoft Project 2000*. Redmond, WA: Microsoft Press.

Cloning (1999). Retrieved June, 2000, from the World Wide Web: http://ucl.broward.cc.fl.us/pathfinders/cloning.htm

Cordero, R. (1991). Managing for speed to avoid product obsolescence: A survey of techniques. *Journal of Product Innovation Management*, *8*, 283-294.

Crawford, M. (1992). The hidden costs of accelerated product development. *Journal of Product Innovation Management*, *9*(3), 188-199.

Crookes, J.G. (1989). Simulation. *Computer modeling for discrete simulation*. Chichester, UK: John Wiley & Sons.

Davis, D.B. (May 1989). Beating the clock. *Electronic Business*, 21.

DeSain, C. (1993). *Drug, device, and diagnostic manufacturing: The ultimate resourcebook.* (2nd ed.). Buffalo Grove, IL: Interpharm Press, Inc.

Dreger, J.B. (1992). *Project management: Effective Scheduling.* New York, NY: Van Nostrand Reinhold.

Dumaine, B. (February 1989). How managers can succeed through speed. *Fortune.*

Emmanuelides, A.P. (October 1991). Sources and strategic significance of product development speed. *1991 PDMA Proceedings*, 20-33.

Ernst & Young, LLP (1999). *Annual Biotechnology Industry Reports*, 1993-1999.

Federal Food & Drug Administration (FDA) (1998). *Guidance for industry: General/Specific use.* Retrieved November 22, 2000, from the World Wide Web: http://www.fda.gov/cdrh/modact/genspec.pdf

Federal Food & Drug Administration (FDA) (2000a). *Clinical trials and Investigational Device Exemption.* Retrieved March 20, 2001, from the World Wide Web: www.fda.gov/cdrh/devadvice/ide/index.shtml

Federal Food & Drug Administration (FDA) (2000b). *Overview of the PMA regulation.* Retrieved May 15, 2001, from the World Wide Web:
http://www.fda.gov/cdrh/dsma/pmaman/sec02.html

Federal Food & Drug Administration (FDA) (2001). *Premarket approval: How to market a PMA medical device.* Retrieved May 20, 2001, from the World Wide Web:
http://www.fda.gov/cdrh/devadvice/316.html#link_2

Fitzgerald, K. (October 1987). Compressing design cycle. *IEEE Spectrum*, 39-44.

Gido, J. (1985). *An introduction to project planning.* Industrial Press, Inc.

Gold, B. (1987). Approaches to accelerating product and process development. *Journal of Product Innovation Management*, *4*(20), 81-88.

Grant, H. (1999). *Development of a research agenda for biomanufacturing.* National Science Foundation Grant 9909874.

Greene, J.H. (1997). *Production and inventory control handbook.* (3rd ed.). New York, NY: McGraw-Hill.

Gupta, A. & Wilemon, D. (1996). Changing patterns in industrial R & D management. *Journal of Product Innovation Management*, *13*, 497-511.

Gupta, A.K., Raj, S.P., & Wilemon, D. (1986). A model for studying R & D-marketing interface in the product innovation process. *Journal of Marketing*, *50*(2), 7-17.

Gupta, A.K. & Wilemon, D.L (1990). Accelerating the development of technology-based new products. *California Management Review*, *32*(2), 24-44.

Guveritz, S. (October 1983). Technology will shorten product life-cycles. *Business Marketing*, 12.

Hauser, J.R. & Clausing, D. (May - June 1988). The house of quality. *Harvard Business Review*, 63-73.

Health Industry Manufacturers Association (1994). *Information document: Biomaterials embargo: Potentially affected permanent implants.*

Hitchcock, J. (2000). *Insulin pumps*. Retrieved September 1, 2000, from the World Wide Web: http://www.childrenwithdiabetes.com/d_06_f00.htm

Joines, J.A., Powell, K.A., & Roberts, S.D. (1992). Object-oriented modeling and simulation in C. In *Proceedings of the 1993 Winter Simulation Conference*, Arlington, VA.

Kelton, W.D., Sadowski, R.P., & Sadowski, D. (1998). *Simulation with Arena*. New York, NY: McGraw-Hill Companies.

Kerzner, H. (1995). *Project Management: A systems approach to planning, scheduling and controlling*. (5th ed). New York, NY: Van Nostrand Reinhold.

King, R. (1987). *Better designs in half the time: Implementing QFD in America*. Methuen, MA, GOAL/QPC.

Kohn, J. (1996). Biomaterials science at a crossroads: Are current product liability laws in the United States hampering innovation and the development of safer medical implants? *Pharmaceutical Research*, *13*(6), 815-819.

Langerak, F., Peelen, E. & Nijssen, E. (1999). A laddering approach to the use of methods and techniques to reduce the cycle time of new-to-the-firm products. *The Journal of Product Innovation Management*, *16*(2), 173-182.

Law, A.M. & Kelton, W.D. (1991). *Simulation modeling and analysis*. (2nd ed.). New York, NY: McGraw-Hill.

Lee, S.M., Moeller, G.L. & Digman, L.A. (1982). *Network analysis for management decisions: A stochastic approach*. Kluwer Nijhoff Publishing.

Leuschner, J. & Rimpler, M. (1990). Preclinical safety testing of plastic products intended for use in man. *Biomedizinisohe Technik, 35*, 44-47.

Lieberman, M. & Montgomery, D. (1988). First mover advantages. *Strategic Management Journal*, 9, 41-58.

McDonough, E.F., III, & Barczak, G. (1991). Speeding up new product development: The effects of leadership style and source of technology. *Journal of Product Innovation Management, 8*, 203-211.

McDonough, E.F., III, & Barczak, G. (1992). The effects of cognitive problem-solving, orientation, and technological familiarity on faster new product development. *Journal of Production Innovation Management, 9*(1), 44-52.

Millson, M., Raj, S., & Wilemon, D. (1992). A survey of major approaches for accelerating new product development. *Journal of Product Innovation Management, 9*(1), 53-69.

Minimed™ User's Guide for Minimed™ Insulin Pump Model 407C.

Modeler, J.J. & Phillips, C.R. (1970). *Project management with CPM and PERT*. Van Nostrand Reinhold Company.

Mongalo, M.A. & Lee, J. (1990). A comparative study of methods for probabilistic project scheduling. *Proceedings of the 12th Annual Conference on Computers and Industrial Engineering, 19*(1-4), 505-509.

Morbey, G.K. (1991). Accelerating the product development process. *1991 PDMA Proceedings*, 34-37.

Nighswonger, G. (1999). Micromachines: A big future for small devices. *Medical Device & Diagnostic Industry, 21*(11), 48-63.

Pegden, C.D., Shannon, R.E., &Sadowski, R.P. (1986). *Introduction to Simulation using SIMAN*. New York, NY: McGraw Hill.

Pidd, M. (1988). *Computer simulation in management science*. (2nd ed). Chichester, UK: John Wiley & Sons.

Pidd, M. (1989). Simulation in Pascal. *Computer modeling for discrete simulation*. (2nd ed). Chichester, UK: John Wiley & Sons.

Pisano, G.P. (1997). *The development factory*. Boston, MA: HBS Press.

Price, J. (1987). The liabilities and consequences of medical device development. *Journal of Biomedical Materials Research: Applied Biomaterials, 21*(A1), 35-58.

Pritsker A.A.B. (1986). *Introduction to Simulation and SLAM II*. (3rd ed.). West Lafayette, IN: Systems Publishing Corporation.

Pritsker, A.A.B. and Happ, W.W. (1966). GERT: Graphical Evaluation and Review Technique Part I: Fundamentals. *The Journal of Industrial Engineering*, *17*(5).

Pritsker, A.A.B. & O'Reilly, J. (1999). *Simulation with Visual SLAM and AweSim*. (2nd ed.). West Lafayette, IN: Systems Publishing Corporation.

Pritsker, A.A.B., Sigal, C.E. & Hammesfahr, R.D.J. (1994). *SLAM II: Network models for decision support*. The Scientific Press.

Rosenau, M.D. (June 1988). Faster new product development. *Journal of Product Innovation Management*, 150-163.

Rosenau, M.D. (1990). *Faster new product development: Getting the right product to market quickly*. New York, NY: AMACOM.

Rosenthal, S.R. & March, A. (1991). Speed to market: Disciplines for product design and development. *Boston University School of Management Manufacturing Roundtable Research Report*.

Ruskin, A.M. & Estes, W.E. (1995). *What every engineer should know about project management*. (2nd ed.). New York, NY: Marcel Dekker, Inc.

Satter, S. & Sordellini, P. (April 1999). EtO sterilization: Microbiological aspects of process validation. *Medical Device & Diagnostic Industry*, *21*(4), 85-98.

Scott, G.M. (2000). Critical technology management issues of new product development in high-tech companies. *The Journal of Product Innovation Management*, *17*, 57-77.

Smith, P.G. (1990). Fast-cycle product development. *Engineering Management Journal*, *2*(2), 11-16.

Spera, G. (1998). Study examines industry leaders. *Medical Device and Diagnostic Industry*, *20*(3), 26.

Symonds, W.C. (October 1991). Pushing design to dizzying speed. *Business Week*, 64-65.

Uttal, B. (March 1987). Speeding new ideas to market. *Fortune*, 62-66.

Verganti, R. (1999). Planned flexibility: Linking anticipation and reaction in product development projects. *Journal of Product Innovation Management*, *16*, 363-376.

Wiest, J. & Levy, F. (1977). *A management guide to PERT/CPM: with GERT/PDM/DCPM and other networks*. New Jersey: Prentice Hall, Inc.

APPENDIX A

OUTPUT ECHO REPORT

```
AweSim Input Translator, version 3.0
Copyright (C) 1999 Symix Systems, Inc.

Reading control BIOM11 ...

   1 GEN,"Dorene Seah","Insulin Pump Product and Process
Development",7/18/00,80,YES,YES;
   2 LIMITS,11,,,3;
   3
INTLC,{{XX[5],0.2},{XX[6],0.3},{XX[7],0.1},{XX[8],0.4},{XX[9],0.1},{XX[
10],0.6},{XX[11],0.3},{XX[1],0.1},{XX[2],0.3},{XX[3],0.4},{XX[4],0.2}};
   4 INITIALIZE,0.0,800,NO,,YES;
   5 NETWORK,READ;
   6 FIN;

BIOM11 successfully read


Translated file BASECASE successfully written
Reading network INS1 - Pass 1...


INS1 - Pass 1 successfully read

Reading network INS1 - Pass 2...


INS1 - Pass 2 successfully read

Reading network INS1 - Pass 3...

   1 START: CREATE,0.0,0.0,,1,1;
   2 ACTIVITY;
   3 TypeSTART: ASSIGN,{{ATRIB[1],1}},1;
   4 ACTIVITY;
   5 ReComponents: GOON,1;
   6 ACTIVITY,1,TRIAG(4,5,6);
   7 RD_1: COLCT,1,FIRSTARRIVE,"Determine Insulin Pump
Components",,,,10;
   8 ACTIVITY;
   9 ACTIVITY,,,,"ReRD_3";
  10 ACTIVITY,,,,"ReRD_4";
  11 ACTIVITY,,,,"ReRD_5";
  12 ACTIVITY,,,,"ReRD_6";
  13 ACTIVITY,,,,"ReRD_7";
  14 ACTIVITY,,,,"ReRD_8";
  15 ACTIVITY,,,,"ReRD_9";
  16 ACTIVITY,,,,"ReRD_10";
  17 ACTIVITY,100,,,"ReRD_11";
  18 ReRD_2: GOON,1;
  19 ACTIVITY,2,TRIAG(2,5,6);
  20 RD_2: COLCT,2,FIRSTARRIVE,"Research and Specify Raw Materials for
Solenoid Motor",,,,1;
  21 ACTIVITY,12,TRIAG(3,5,6);
  22 RD_12: COLCT,12,FIRSTARRIVE,"Test for Suitability of Raw Materials
for Solenoid Motor",,,,1;
  23 ACTIVITY,42,,PROB(0.1),"ReRD_2";
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  24 ACTIVITY,32,,PROB(0.9);
  25 Split1: GOON,1;
  26 ACTIVITY,,,ATRIB[1]==1;
  27 ACTIVITY,,,ATRIB[1]==3,"ReProd";
  28 ACTIVITY,,,ATRIB[1]==2,"ReProd";
  29 Accum1: ACCUMULATE,10,10,LAST,1;
  30 ACTIVITY;
  31 ReProd: GOON,1;
  32 ACTIVITY,144,TRIAG(5,7,8);
  33 RD_22: COLCT,22,FIRSTARRIVE,"Determine Production Assembly
Process",,,,2;
  34 ACTIVITY;
  35 ACTIVITY,53,TRIAG(12,13,15),,"MFG_1";
  36 ReSterilization: GOON,1;
  37 ACTIVITY,52,TRIAG(5,7,8);
  38 RD_23: COLCT,23,FIRSTARRIVE,"Determine Sterilization Method",,,,1;
  39 ACTIVITY,54,TRIAG(2,5,6);
  40 RD_24: COLCT,24,FIRSTARRIVE,"Analyze Effects of
Sterilization",,,,1;
  41 ACTIVITY,58,,PROB(0.2),"ReSterilization";
  42 ACTIVITY,57,TRIAG(2,4,6),PROB(0.8);
  43 RD_25: COLCT,25,FIRSTARRIVE,"Analyze Particulate
Contaminants",,,,1;
  44 ACTIVITY,61,,PROB(0.4),"ReSterilization";
  45 ACTIVITY,60,,PROB(0.6);
  46 Split2: GOON,3;
  47 ACTIVITY;
  48 ACTIVITY,65,TRIAG(1,2,3),,"RD_27";
  49 ACTIVITY,,,,"RePackaging";
  50 ReBiocompatibility: GOON,1;
  51 ACTIVITY,60,TRIAG(1,5,6);
  52 RD_26: COLCT,26,FIRSTARRIVE,"Run Tests to Investigate
Biocompatibility",,,,1;
  53 ACTIVITY,62,TRIAG(2,5,8);
  54 RD_29: COLCT,27,FIRStARRIVE,"Perform Failure-Mode-Effect
Analysis",,,,1;
  55 ACTIVITY,74,,ATRIB[1]==2;
  56 ACTIVITY,74,,ATRIB[1]==3;
  57 ACTIVITY,64,,ATRIB[1]==1,"Split3";
  58 Split4: GOON,1;
  59 ACTIVITY,98,,PROB(0.3),"ReComponents";
  60 ACTIVITY,75,,PROB(0.3),"RePMN";
  61 ACTIVITY,76,,PROB(0.4),"ReProdProcess";
  62 Split3: GOON,1;
  63 ACTIVITY,72,,PROB(0.2),"ReComponents";
  64 ACTIVITY,73,,PROB(0.8);
  65 Accum2: ACCUMULATE,3,1,LAST,1;
  66 ACTIVITY;
  67 Accum3: ACCUMULATE,2,1,LAST,1;
  68 ACTIVITY;
  69 ReProdProcess: GOON,1;
  70 ACTIVITY,78,TRIAG(5,6,7);
  71 MFG_4: COLCT,34,FIRSTARRIVE,"Establish Formal Production
Process",,,,1;
  72 ACTIVITY,79,TRIAG(1,3,5);
  73 MFG_5: COLCT,35,FIRSTARRIVE,"Determine Batch Size and Frequency of
Manufacturing",,,,1;
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  74 ACTIVITY,80,TRIAG(2,3,4);
  75 MFG_6: COLCT,36,FIRSTARRIVE,"Discuss with Research Team and
Confirm Each Step of Production Process",,,1;
  76 ACTIVITY,96,,PROB(0.1),"ReProdProcess";
  77 ACTIVITY,82,TRIAG(3,6,10),PROB(0.9);
  78 MFG_7: COLCT,37,FIRSTARRIVE,"Propose New Techniques and Equipment
for Scale-Up Manufacturing",,,1;
  79 ACTIVITY;
  80 ReManufacture: GOON,1;
  81 ACTIVITY,83,TRIAG(7,8,12);
  82 MFG_8: COLCT,38,FIRSTARRIVE,"Manufacture Insulin Pump
Components",,,1;
  83 ACTIVITY;
  84 ReMFG_9: GOON,1;
  85 ACTIVITY,84,TRIAG(2,7,9);
  86 MFG_9: COLCT,39,FIRSTARRIVE,"Assemble Solenoid Motor",,,1;
  87 ACTIVITY,85,TRIAG(1,5,7);
  88 MFG_10: COLCT,40,FIRSTARRIVE,"Test Solenoid Motor",,,1;
  89 ACTIVITY,97,,PROB(0.2),"ReMFG_9";
  90 ACTIVITY,87,,PROB(0.8);
  91 ReMFG_11: GOON,1;
  92 ACTIVITY,87,TRIAG(2,5,6);
  93 MFG_11: COLCT,41,FIRSTARRIVE,"Assemble Electronics Board",,,1;
  94 ACTIVITY,88,TRIAG(4,6,8);
  95 MFG_12: COLCT,42,FIRSTARRIVE,"Test Electronics Board",,,1;
  96 ACTIVITY,91,,PROB(0.3),"ReMFG_11";
  97 ACTIVITY,90,,PROB(0.7);
  98 ReMFG_13: GOON,1;
  99 ACTIVITY,90,TRIAG(3,6,7);
 100 MFG_13: COLCT,43,FIRSTARRIVE,"Assemble Solenoid Motor and
Electronics on Pump Case",,,1;
 101 ACTIVITY,92,TRIAG(1,4,5);
 102 MFG_14: COLCT,44,FIRSTARRIVE,"Test Solenoid Motor and Electronics
on Pump Case",,,1;
 103 ACTIVITY,95,,PROB(0.2),"ReMFG_13";
 104 ACTIVITY,94,,PROB(0.8);
 105 ReMFG_15: GOON,1;
 106 ACTIVITY,94,TRIAG(2,3,4);
 107 MFG_15: COLCT,45,FIRSTARRIVE,"Assemble Final Product",,,1;
 108 ACTIVITY,99,TRIAG(2,4,5);
 109 MFG_16: COLCT,46,FIRSTARRIVE,"Test Final Product",,,1;
 110 ACTIVITY,101,,ATRIB[1]==1;
 111 ACTIVITY,104,,ATRIB[1]==3,"Split6";
 112 ACTIVITY,104,,ATRIB[1]==2,"Split6";
 113 Split5: GOON,1;
 114 ACTIVITY,102,,PROB(0.1),"ReMFG_15";
 115 ACTIVITY,103,,PROB(0.9);
 116 ReMFG_17: GOON,1;
 117 ACTIVITY,103,TRIAG(3,6,7);
 118 MFG_17: COLCT,47,FIRSTARRIVE,"Validate Insulin Pump Processing
Events",,,1;
 119 ACTIVITY;
 120 ReEnvironment: GOON,1;
 121 ACTIVITY,109,TRIAG(3,5,6);
 122 MFG_18: COLCT,48,FIRSTARRIVE,"Ensure Environmental Controls Follow
Regulations",,,1;
 123 ACTIVITY,112,,ATRIB[1]==1;
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124 ACTIVITY,113,,ATRIB[1]==2,"Split7";
125 ACTIVITY,113,,ATRIB[1]==3,"Split7";
126 ReIA: GOON,1;
127 ACTIVITY,112,TRIAG(4,6,7);
128 REG_1: COLCT,49,FIRSTARRIVE,"File for Investigational Approval by
IRB",,,,1;
129 ACTIVITY,115,TRIAG(2,3,4);
130 Split8: GOON,1;
131 ACTIVITY,116,,PROB(0.1),"ReIA";
132 ACTIVITY,117,,PROB(0.9);
133 ReIDE: GOON,1;
134 ACTIVITY,117,TRIAG(5,7,8);
135 REG_2: COLCT,50,FIRSTARRIVE,"Submit Investigational Device
Exemption to FDA",,,,1;
136 ACTIVITY,118,TRIAG(4,5,6);
137 Split9: GOON,1;
138 ACTIVITY,120,,PROB(0.2),"ReIDE";
139 ACTIVITY,119,,PROB(0.8);
140 ReMFG_19: GOON,1;
141 ACTIVITY,119,TRIAG(5,8,9);
142 MFG_19: COLCT,51,FIRSTARRIVE,"Perform Clinical Testing",,,,1;
143 ACTIVITY;
144 RePMN: GOON,1;
145 ACTIVITY,121,TRIAG(3,4,5);
146 REG_3: COLCT,52,FIRSTARRIVE,"Submit Premarket Notification
510K",,,,1;
147 ACTIVITY,,TRIAG(8,9,10);
148 Split10: GOON,1;
149 ACTIVITY,123,,ATRIB[1]==1;
150 ACTIVITY,124,,ATRIB[1]==3,"TypeMFG1";
151 ACTIVITY,125,,ATRIB[1]==2,"TypeRD1";
152 Split11: GOON,1;
153 ACTIVITY,148,,PROB(XX[1]),"ReMFG_19";
154 ACTIVITY,149,,PROB(XX[2]),"ReRD";
155 ACTIVITY,150,,PROB(XX[3]),"ReMFG";
156 ACTIVITY,127,,PROB(XX[4]);
157 Market: GOON,1;
158 ACTIVITY,114,TRIAG(2,3,4);
159 PREPAREMARKET: COLCT,53,FIRSTARRIVE,"Prepare Insulin Pump for
Market",,,,1;
160 ACTIVITY,127;
161 READYMARKET: COLCT,54,FIRSTARRIVE,"Insulin Pump Ready for
Market",40,100,10,1;
162 ACTIVITY;
163 END: TERMINATE,1;
164 TypeMFG1:
ASSIGN,{{XX[1],0.1},{XX[2],0.1},{XX[3],0.1},{XX[4],0.7}},1;
165 ACTIVITY;
166 Split13: GOON,1;
167 ACTIVITY,133,,PROB(XX[1]),"ReMFG_19";
168 ACTIVITY,129,,PROB(XX[4]),"Market";
169 ACTIVITY,136,,PROB(XX[2]);
170 ACTIVITY,135,,PROB(XX[3]),"TypeMFG3";
171 TypeRD3:
ASSIGN,{{XX[5],0.4},{XX[6],0.2},{XX[7],0.3},{XX[8],0.1}},1;
172 ACTIVITY;
173 ReRD: GOON,1;
```

```
174 ACTIVITY;
175 TypeRD: ASSIGN,{{ATRIB[1],2}},1;
176 ACTIVITY,137,,PROB(XX[5]);
177 ACTIVITY,140,,PROB(XX[8]),"ReBiocompatibility";
178 ACTIVITY,139,,PROB(XX[7]),"ReSterilization";
179 ACTIVITY,138,,PROB(XX[6]),"RepeatProd";
180 RepeatRaw: COLCT,55,FIRSTARRIVE,"ReRawFrReRD",,,,1;
181 ACTIVITY;
182 ReRaw: GOON,1;
183 ACTIVITY,150,,PROB(0.1),"ReRD_2";
184 ACTIVITY,159,,PROB(0.1),"ReRD_11";
185 ACTIVITY,158,,PROB(0.1),"ReRD_10";
186 ACTIVITY,157,,PROB(0.1),"ReRD_9";
187 ACTIVITY,156,,PROB(0.1),"ReRD_8";
188 ACTIVITY,155,,PROB(0.1),"ReRD_7";
189 ACTIVITY,154,,PROB(0.1),"ReRD_6";
190 ACTIVITY,153,,PROB(0.1),"ReRD_5";
191 ACTIVITY,152,,PROB(0.1),"ReRD_4";
192 ACTIVITY,151,,PROB(0.1),"ReRD_3";
193 RepeatProd: COLCT,56,FIRSTARRIVE,"ReProdFrReRD",,,,1;
194 ACTIVITY,,,,"ReProd";
195 TypeMFG3: ASSIGN,{{XX[9],0.1},{XX[10],0.2},{XX[11],0.7}},1;
196 ACTIVITY;
197 ReMFG: GOON,1;
198 ACTIVITY;
199 TypeMFG: ASSIGN,{{ATRIB[1],3}},1;
200 ACTIVITY,141,,PROB(XX[9]);
201 ACTIVITY,143,,PROB(XX[11]),"ReProdProcess";
202 ACTIVITY,142,,PROB(XX[10]),"ReEnvironment";
203 RepeatManufacture:
COLCT,57,FIRSTARRIVE,"ReManufactureFrReMFG",,,,1;
204 ACTIVITY,,,,"ReManufacture";
205 TypeRD1:
ASSIGN,{{XX[1],0.08},{XX[2],0.03},{XX[3],0.03},{XX[4],0.86}},1;
206 ACTIVITY;
207 Split12: GOON,1;
208 ACTIVITY,145,,PROB(XX[1]),"ReMFG_19";
209 ACTIVITY,128,,PROB(XX[4]),"Market";
210 ACTIVITY,146,,PROB(XX[2]);
211 ACTIVITY,147,,PROB(XX[3]),"TypeMFG2";
212 TypeRD2:
ASSIGN,{{XX[5],0.1},{XX[6],0.1},{XX[7],0.5},{XX[8],0.3}},1;
213 ACTIVITY,,,,"ReRD";
214 TypeMFG2: ASSIGN,{{XX[9],0.2},{XX[10],0.3},{XX[11],0.5}},1;
215 ACTIVITY,,,,"ReMFG";
216 Split7: GOON,1;
217 ACTIVITY,114,,PROB(0.3),"ReIA";
218 ACTIVITY,113,,PROB(0.7),"RePMN";
219 Split6: GOON,1;
220 ACTIVITY,106,,PROB(0.1),"ReMFG_15";
221 ACTIVITY,107,,PROB(0.1),"ReMFG_17";
222 ACTIVITY,108,,PROB(0.8),"RePMN";
223 RD_27: COLCT,28,FIRSTARRIVE,"Identify Storage Criteria",,,,1;
224 ACTIVITY,,,,"Accum2";
225 RePackaging: GOON,1;
226 ACTIVITY,67,TRIAG(1,2,3);
227 RD_28: COLCT,29,FIRSTARRIVE,"Identify Packaging Material",,,,1;
```

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228 ACTIVITY,68,TRIAG(1,2,3);
229 RD_30: COLCT,30,FIRSTARRIVE,"Evaluate Packaging Material",,,1;
230 ACTIVITY,71,,PROB(0.2),"RePackaging";
231 ACTIVITY,70,,PROB(0.8),"Accum2";
232 MFG_1: COLCT,31,FIRSTARRIVE,"Construct Preliminary GMP
Manufacturing Facility",,,,1;
233 ACTIVITY,55,TRIAG(4,5,6);
234 MFG_2: COLCT,32,FIRSTARRIVE,"Identify and Qualify Alternate
Vendors",,,,1;
235 ACTIVITY,77,TRIAG(3,4,5);
236 MFG_3: COLCT,33,FIRSTARRIVE,"Install New Equipment",,,,1;
237 ACTIVITY,,,,"Accum3";
238 ReRD_3: GOON,1;
239 ACTIVITY,3,TRIAG(1,3,6);
240 RD_3: COLCT,3,FIRSTARRIVE,"Research and Specify Raw Materials for
Syringe",,,,1;
241 ACTIVITY,13,TRIAG(1,4,5);
242 RD_13: COLCT,13,FIRSTARRIVE,"Test for Suitability of Raw Materials
for Syringe",,,,1;
243 ACTIVITY,43,,PROB(0.1),"ReRD_3";
244 ACTIVITY,33,,PROB(0.9),"Split1";
245 ReRD_4: GOON,1;
246 ACTIVITY,4,TRIAG(3,5,6);
247 RD_4: COLCT,4,FIRSTARRIVE,"Research and Specify Raw Materials for
Pump Case",,,,1;
248 ACTIVITY,14,TRIAG(2,4,5);
249 RD_14: COLCT,14,FIRSTARRIVE,"Test for Suitability of Raw Materials
for Pump Case",,,,1;
250 ACTIVITY,44,,PROB(0.1),"ReRD_4";
251 ACTIVITY,34,,PROB(0.9),"Split1";
252 ReRD_5: GOON,1;
253 ACTIVITY,5,TRIAG(2,3,5);
254 RD_5: COLCT,5,FIRSTARRIVE,"Research and Specify Raw Materials for
Window Panel",,,,1;
255 ACTIVITY,15,TRIAG(3,4,8);
256 RD_15: COLCT,15,FIRSTARRIVE,"Test for Suitability of Raw Materials
for Window Panel",,,,1;
257 ACTIVITY,45,,PROB(0.1),"ReRD_5";
258 ACTIVITY,35,,PROB(0.9),"Split1";
259 ReRD_6: GOON,1;
260 ACTIVITY,6,TRIAG(4,6,8);
261 RD_6: COLCT,6,FIRSTARRIVE,"Research and Specify Raw Materials for
Mechanical Driver Arm",,,,1;
262 ACTIVITY,16,TRIAG(1,4,8);
263 RD_16: COLCT,16,FIRSTARRIVE,"Test for Suitability of Raw Materials
for Mechanical Driver Arm",,,,1;
264 ACTIVITY,46,,PROB(0.1),"ReRD_6";
265 ACTIVITY,36,,PROB(0.9),"Split1";
266 ReRD_7: GOON,1;
267 ACTIVITY,7,TRIAG(1,5,9);
268 RD_7: COLCT,7,FIRSTARRIVE,"Research and Specify Raw Materials for
Lead Screw",,,,1;
269 ACTIVITY,17,TRIAG(3,5,6);
270 RD_17: COLCT,17,FIRSTARRIVE,"Test for Suitability of Raw Materials
for Lead Screw",,,,1;
271 ACTIVITY,47,,PROB(0.1),"ReRD_7";
272 ACTIVITY,37,,PROB(0.9),"Split1";
```

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 273 ReRD_8: GOON,1;
 274 ACTIVITY,8,TRIAG(2,6,7);
 275 RD_8: COLCT,8,FIRSTARRIVE,"Research and Specify Raw Materials for
Reservoir Converter",,,,1;
 276 ACTIVITY,18,TRIAG(2,5,8);
 277 RD_18: COLCT,18,FIRSTARRIVE,"Test for Suitability of Raw Materials
for Reservoir Converter",,,,1;
 278 ACTIVITY,48,,PROB(0.1),"ReRD_8";
 279 ACTIVITY,38,,PROB(0.9),"Split1";
 280 ReRD_9: GOON,1;
 281 ACTIVITY,9,TRIAG(1,4,9);
 282 RD_9: COLCT,9,FIRSTARRIVE,"Research and Specify Raw Materials for
Luer Neck Lever",,,,1;
 283 ACTIVITY,19,TRIAG(2,3,4);
 284 RD_19: COLCT,19,FIRSTARRIVE,"Test for Suitability of Raw Materials
for Luer Neck Lever",,,,1;
 285 ACTIVITY,49,,PROB(0.1),"ReRD_9";
 286 ACTIVITY,39,,PROB(0.9),"Split1";
 287 ReRD_10: GOON,1;
 288 ACTIVITY,10,TRIAG(2,4,5);
 289 RD_10: COLCT,10,FIRSTARRIVE,"Research and Specify Raw Materials
for Battery Compartment",,,,1;
 290 ACTIVITY,20,TRIAG(3,7,8);
 291 RD_20: COLCT,20,FIRSTARRIVE,"Test for Suitability of Raw Materials
for Battery Compartment",,,,1;
 292 ACTIVITY,50,,PROB(0.1),"ReRD_10";
 293 ACTIVITY,40,,PROB(0.9),"Split1";
 294 ReRD_11: GOON,1;
 295 ACTIVITY,11,TRIAG(7,8,9);
 296 RD_11: COLCT,11,FIRSTARRIVE,"Develop Code for Software",,,,1;
 297 ACTIVITY,21,TRIAG(2,3,5);
 298 RD_21: COLCT,21,FIRSTARRIVE,"Test Software Code",,,,1;
 299 ACTIVITY,51,,PROB(0.1),"ReRD_11";
 300 ACTIVITY,41,,PROB(0.9),"Split1";

INS1 - Pass 3 successfully read


Translated network file BASECASE.TRN successfully written
```

APPENDIX B

OUTPUT INTERMEDIATE REPORT

```
AweSim Simulator, version 3.0
Copyright (C) 1996 Pritsker Corporation


Translated file BASECASE successfully read

Translated file BASECASE.TRN successfully read


        ** AweSim Version 3.0 ECHO REPORT **
        Thu May 31 16:35:20 2001


  Simulation Project : Insulin Pump Product and Process Development
  Modeler : Dorene Seah
  Date : 7/18/00

Run options
        Run number 1 of 80
        Beginning time of run : 0.000000
        Ending time of run    : 800.000000
        Maximum errors during run  : 1
        Maximum entities in system : 300
        Clear statistics between runs : NO
        Execute simulation after input: YES
        Warn of destroyed entities    : YES
        Generate summary report : EVERY(1)

Variables
        Number of LL variables : 0
        Number of XX variables : 12
        Number of SZ variables : 0
        Number of entity ATRIBs: 4
        Number of entity LTRIBs: 0
        Number of entity STRIBs: 0

Collect Information

COLCT     IDENTIFIER          HISTOGRAM SPECIFICATIONS
NUMBER                        NCEL       HLOW       HWID

    1     Determine Insuli      0         0.0000     0.0000
    2     Research and Spe      0         0.0000     0.0000
    3     Research and Spe      0         0.0000     0.0000
    4     Research and Spe      0         0.0000     0.0000
    5     Research and Spe      0         0.0000     0.0000
    6     Research and Spe      0         0.0000     0.0000
    7     Research and Spe      0         0.0000     0.0000
    8     Research and Spe      0         0.0000     0.0000
    9     Research and Spe      0         0.0000     0.0000
   10     Research and Spe      0         0.0000     0.0000
   11     Develop Code for      0         0.0000     0.0000
   12     Test for Suitabi      0         0.0000     0.0000
   13     Test for Suitabi      0         0.0000     0.0000
   14     Test for Suitabi      0         0.0000     0.0000
   15     Test for Suitabi      0         0.0000     0.0000
   16     Test for Suitabi      0         0.0000     0.0000
```

17	Test for Suitabi	0	0.0000	0.0000
18	Test for Suitabi	0	0.0000	0.0000
19	Test for Suitabi	0	0.0000	0.0000
20	Test for Suitabi	0	0.0000	0.0000
21	Test Software Co	0	0.0000	0.0000
22	Determine Produc	0	0.0000	0.0000
23	Determine Steril	0	0.0000	0.0000
24	Analyze Effects	0	0.0000	0.0000
25	Analyze Particul	0	0.0000	0.0000
26	Run Tests to Inv	0	0.0000	0.0000
27	Perform Failure-	0	0.0000	0.0000
28	Identify Storage	0	0.0000	0.0000
29	Identify Packagi	0	0.0000	0.0000
30	Evaluate Packagi	0	0.0000	0.0000
31	Construct Prelim	0	0.0000	0.0000
32	Identify and Qua	0	0.0000	0.0000
33	Install New Equi	0	0.0000	0.0000
34	Establish Formal	0	0.0000	0.0000
35	Determine Batch	0	0.0000	0.0000
36	Discuss with Res	0	0.0000	0.0000
37	Propose New Tech	0	0.0000	0.0000
38	Manufacture Insu	0	0.0000	0.0000
39	Assemble Solenoi	0	0.0000	0.0000
40	Test Solenoid Mo	0	0.0000	0.0000
41	Assemble Electro	0	0.0000	0.0000
42	Test Electronics	0	0.0000	0.0000
43	Assemble Solenoi	0	0.0000	0.0000
44	Test Solenoid Mo	0	0.0000	0.0000
45	Assemble Final P	0	0.0000	0.0000
46	Test Final Produ	0	0.0000	0.0000
47	Validate Insulin	0	0.0000	0.0000
48	Ensure Environme	0	0.0000	0.0000
49	File for Investi	0	0.0000	0.0000
50	Submit Investiga	0	0.0000	0.0000
51	Perform Clinical	0	0.0000	0.0000
52	Submit Premarket	0	0.0000	0.0000
53	Prepare Insulin	0	0.0000	0.0000
54	Insulin Pump Rea	0	0.0000	0.0000
55	ReRawFrReRD	0	0.0000	0.0000
56	ReProdFrReRD	0	0.0000	0.0000
57	ReManufactureFrR	0	0.0000	0.0000

Random Number Streams Information

STREAM NUMBER	SEED VALUE	REINITIALIZATION OF STREAM
1	428956419	NO
2	1954324947	NO
3	1145661099	NO
4	1835732737	NO
5	794161987	NO
6	1329531353	NO
7	200496737	NO
8	633816299	NO
9	1410143363	NO
10	1282538739	NO
11	794026294	NO

12	977821281	NO
13	699858332	NO
14	1683733431	NO
15	96358723	NO
16	602885281	NO
17	871633513	NO
18	1984612552	NO
19	232391877	NO
20	135618479	NO
21	1814383333	NO
22	324184021	NO
23	1667630903	NO
24	1082038467	NO
25	1885999711	NO
26	111454913	NO
27	1262746665	NO
28	725514806	NO
29	2087308334	NO
30	1027457115	NO
31	1716773784	NO
32	1417840845	NO
33	1401170757	NO
34	505042365	NO
35	1554339362	NO
36	1747494519	NO
37	93505551	NO
38	194910479	NO
39	1297383121	NO
40	806401626	NO
41	1242558033	NO
42	1722906649	NO
43	1195299681	NO
44	57081438	NO
45	817128895	NO
46	1919094954	NO
47	1435250780	NO
48	1278785392	NO
49	1309679730	NO
50	1281484595	NO
51	394601628	NO
52	85886326	NO
53	1571729619	NO
54	918904909	NO
55	1864761823	NO
56	1268956513	NO
57	1034484093	NO
58	1763605842	NO
59	1039242913	NO
60	1322164949	NO
61	1783293536	NO
62	70884048	NO
63	1420035359	NO
64	994868838	NO
65	1463578868	NO
66	790460117	NO
67	1431310689	NO
68	268966977	NO

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 69        1446647089    NO
 70        1990098112    NO
 71         893770676    NO
 72         756136149    NO
 73        1758938931    NO
 74        1098677441    NO
 75        1178898083    NO
 76         271054147    NO
 77        1009598300    NO
 78        2114861268    NO
 79        1617952069    NO
 80        1131840250    NO
 81        2094070757    NO
 82         195319339    NO
 83        1659214966    NO
 84        1440396285    NO
 85         563832118    NO
 86        1702510512    NO
 87        1721643437    NO
 88        2054527950    NO
 89         231008758    NO
 90         811760922    NO
 91         931421337    NO
 92        2056682338    NO
 93        1224747865    NO
 94        2087343551    NO
 95         434301072    NO
 96        1002794063    NO
 97        1132277789    NO
 98        1505059305    NO
 99         208486230    NO
100        1769772683    NO

Intermediate results for run 1
 Maximum number of entities concurrently in system is 12

Intermediate results for run 2
 Maximum number of entities concurrently in system is 10

Intermediate results for run 3
 Maximum number of entities concurrently in system is 10

Intermediate results for run 4
 Maximum number of entities concurrently in system is 10

Intermediate results for run 5
 Maximum number of entities concurrently in system is 10

Intermediate results for run 6
 Maximum number of entities concurrently in system is 12

Intermediate results for run 7
 Maximum number of entities concurrently in system is 10

Intermediate results for run 8
 Maximum number of entities concurrently in system is 10
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```
Intermediate results for run 9
 Maximum number of entities concurrently in system is 10

Intermediate results for run 10
 Maximum number of entities concurrently in system is 10

Intermediate results for run 11
 Maximum number of entities concurrently in system is 10

Intermediate results for run 12
 Maximum number of entities concurrently in system is 10

Intermediate results for run 13
 Maximum number of entities concurrently in system is 10

Intermediate results for run 14
 Maximum number of entities concurrently in system is 10

Intermediate results for run 15
 Maximum number of entities concurrently in system is 10

Intermediate results for run 16
 Maximum number of entities concurrently in system is 10

Intermediate results for run 17
 Maximum number of entities concurrently in system is 10

Intermediate results for run 18
 Maximum number of entities concurrently in system is 10

Intermediate results for run 19
 Maximum number of entities concurrently in system is 12

Intermediate results for run 20
 Maximum number of entities concurrently in system is 10

Intermediate results for run 21
 Maximum number of entities concurrently in system is 92

Intermediate results for run 22
 Maximum number of entities concurrently in system is 10

Intermediate results for run 23
 Maximum number of entities concurrently in system is 10

Intermediate results for run 24
 Maximum number of entities concurrently in system is 10

Intermediate results for run 25
 Maximum number of entities concurrently in system is 10

Intermediate results for run 26
 Maximum number of entities concurrently in system is 10

Intermediate results for run 27
 Maximum number of entities concurrently in system is 10
```

```
Intermediate results for run 28
 Maximum number of entities concurrently in system is 10

Intermediate results for run 29
 Maximum number of entities concurrently in system is 10

Intermediate results for run 30
 Maximum number of entities concurrently in system is 10

Intermediate results for run 31
 Maximum number of entities concurrently in system is 12

Intermediate results for run 32
 Maximum number of entities concurrently in system is 10

Intermediate results for run 33
 Maximum number of entities concurrently in system is 10

Intermediate results for run 34
 Maximum number of entities concurrently in system is 10

Intermediate results for run 35
 Maximum number of entities concurrently in system is 46

Intermediate results for run 36
 Maximum number of entities concurrently in system is 10

Intermediate results for run 37
 Maximum number of entities concurrently in system is 10

Intermediate results for run 38
 Maximum number of entities concurrently in system is 12

Intermediate results for run 39
 Maximum number of entities concurrently in system is 10

Intermediate results for run 40
 Maximum number of entities concurrently in system is 10

Intermediate results for run 41
 Maximum number of entities concurrently in system is 10

Intermediate results for run 42
 Maximum number of entities concurrently in system is 10

Intermediate results for run 43
 Maximum number of entities concurrently in system is 10

Intermediate results for run 44
 Maximum number of entities concurrently in system is 10

Intermediate results for run 45
 Maximum number of entities concurrently in system is 10

Intermediate results for run 46
 Maximum number of entities concurrently in system is 10
```

```
Intermediate results for run 47
 Maximum number of entities concurrently in system is 10

Intermediate results for run 48
 Maximum number of entities concurrently in system is 34

Intermediate results for run 49
 Maximum number of entities concurrently in system is 59

Intermediate results for run 50
 Maximum number of entities concurrently in system is 10

Intermediate results for run 51
 Maximum number of entities concurrently in system is 10

Intermediate results for run 52
 Maximum number of entities concurrently in system is 10

Intermediate results for run 53
 Maximum number of entities concurrently in system is 10

Intermediate results for run 54
 Maximum number of entities concurrently in system is 10

Intermediate results for run 55
 Maximum number of entities concurrently in system is 10

Intermediate results for run 56
 Maximum number of entities concurrently in system is 10

Intermediate results for run 57
 Maximum number of entities concurrently in system is 10

Intermediate results for run 58
 Maximum number of entities concurrently in system is 12

Intermediate results for run 59
 Maximum number of entities concurrently in system is 10

Intermediate results for run 60
 Maximum number of entities concurrently in system is 10

Intermediate results for run 61
 Maximum number of entities concurrently in system is 10

Intermediate results for run 62
 Maximum number of entities concurrently in system is 10

Intermediate results for run 63
 Maximum number of entities concurrently in system is 10

Intermediate results for run 64
 Maximum number of entities concurrently in system is 12

Intermediate results for run 65
 Maximum number of entities concurrently in system is 10
```

```
 Intermediate results for run 66
  Maximum number of entities concurrently in system is 59

 Intermediate results for run 67
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 68
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 69
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 70
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 71
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 72
  Maximum number of entities concurrently in system is 96

 Intermediate results for run 73
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 74
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 75
  Maximum number of entities concurrently in system is 97

 Intermediate results for run 76
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 77
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 78
  Maximum number of entities concurrently in system is 54

 Intermediate results for run 79
  Maximum number of entities concurrently in system is 10

 Intermediate results for run 80
  Maximum number of entities concurrently in system is 10


0 total errors during execution
```

listing for textual representation or a tree diagram, for graphical representation. According to Dreger (1992) and Ruskin and Estes (1995), some project managers have the tendency to skip this phase in order to save time. However, the overall costs of the project will be higher if the planning phase is improperly coordinated.

a project plan. They include a
s used, policies and procedures,
e requirements, performance
g, and auditing.

y analysis of human resources,
Critical Path Method (CPM),
Gantt charts, as well as tracking
oject scheduling, a *network* is
g or ending point for a group of
ceed from one event or point in
nown in Figure 2. The circles,
ranches, represent activities. In
es. The number over the arrow
ther event. Under each arrow is