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FDA REGULATORY ACTIONS:
Protecting the Consumer

An Interactive Qualifying Project Report
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ABSTRACT

This Interactive Qualifying Project (IQP) sets forth guidelines and offers advice as to how companies can increase the success rates for the approval of their products during clinical trials with the aim of attaining and maintaining Food and Drug Administration (FDA) approval. FDA actions against non-conforming products and corporation were studied. Advice concerning validation considerations throughout the entire approval process and beyond was addressed with special attention to current Good Manufacturing Practices (cGMP's) and software/control system validation. The societal and economic impacts of the entire regulatory affair were examined centering upon pharmaceuticals, including Zomax, EPO, Triazure, Vasotec, Serc and Pulmozyme, including the integratory effects of improved approval success rates.

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1. INTRODUCTION

Prior to the 20th century, a need for the regulation of the food and drug industries had existed but was never addressed due to the microeconomic environment in which the sales of medicines, medical devices and cosmetics, both real and fraudulent, had encompassed. As the businesses and numbers of individuals dealing in this trade expanded, the need for the substantiation of claims by the industry and regulation of the manufactured products became imperative with the ever-increasing instances of fraud and injury resulting from these unregulated products. The expansion of railroads and roadways coupled with the industrial revolution allowed for the distribution of products throughout the United States (US). Foreign products fell under federal regulatory sanctions during the mid-19th century as a reactionary measure to the poisoning of US soldiers with contaminated Mexican quinine water used for the assuagement of malaria (Patrick, 1988). The resulting regulations demanded that all imported drugs be verified by meeting the standards set about in the US Pharmacopeia (the US reference guide stating the dose strengths, properties, purity and criteria of drugs and medicinal preparations). Laws regulating the production and sale of drugs domestically took another 50 years to usher in the realization that capitalism and entrepreneurship were not looking out for the benefit of society. In the thirty years prior to 1906 more than 190 laws were proposed to the congress of the United States in order to protect the consumer; however, none of these laws were passed (Patrick, 1988). All of these proposed laws stemmed from the growing number of documented cases of addictions and poisonings of consumers as well as adulterations and fraudulence of products by the drug industry. The

most radical and vocal of cries arose from the author Upton Sinclair whose documentary The Jungle illuminated the unsanitary and horrendous conditions found in a Chicago meat processing plant (Sinclair, 1905). Published in 1905, Sinclair's The Jungle forced President Theodore Roosevelt, via the upsurgent cries of the people in response to this documentary, to address Congress and urge its members to approve legislature regulating domestic food and drugs intended for interstate commerce. The Congress of 1906 approved the federal Pure Food and Drug Act of 1906, which federally outlawed the mislabeling and adulteration of food, drug, cosmetics, and drinks sold or distributed interstate. A division of the Department of Agriculture, the Bureau of Chemistry, was given the power to dictate and enforce this act. The Pure Food and Drug Act of 1906 would become the foundation upon which the Food and Drug Administration (FDA) would be built.

Today, the Food and Drug Administration enforces over half a dozen federal acts that ensure the safety, purity, labeling, and effectiveness of drug products and medical devices. Over the past nine decades, modern medicine and science have made vast strides in the creation of new and more effective drugs for the treatment and prevention of disease. This progress continues at a dizzying pace. In the interest of public health, the progress has been paralleled closely with the need for effective regulation of the development and manufacture of these products. The FDA has developed guidelines, procedures and standards outlined in the Code of Federal Regulations 21 for gaining FDA approval prior to the manufacture and marketing of a product as well as maintenance of compliance beyond this initial approval. An integral section of the CFR

21 is the current Good Manufacturing Practices (cGMP's) of the FDA that were first issued in 1963. With the force of the law behind them, the goal of the GMP regulations is to safeguard the consumer against unsafe, impure, and ineffective drug products. The FDA regularly proposes and incorporates revisions to the cGMP's as technology advances and industrial practices are updated to ensure that these regulations remain current.

Vying for approval, the safety and efficacy of all investigational drugs, as well as the potency and purity of the product must be demonstrated by the manufacturer or sponsor. In addition, all products must be labeled according to FDA specification stating the appropriate dosage, warnings, directions, and ingredient composition. The procedures specified for attaining approval for a pharmaceutical, medical or biotechnological product is a multi-step process consisting of three phases of trials, each expanding upon the assurance that the product under examination meets FDA standards. These trials are documented in the Investigational New Drug Application (IND) for the product, which are revised as the product progresses through clinical trials by the company sponsoring or producing the product under evaluation. Epogen by Amgen, Inc., Pulmozyme by Genentech, Inc., and Vasotec by Merck & Co., Inc. are biotechnological and pharmaceutical successes in both clinical trials and subsequent final approval by the FDA. These overwhelming successes are a result of careful and extensive trials, extensive validation exercises prior to audit, and strong demand for such products. However, many products lack the success that these products experienced. Products such as Zomax by McNeil Pharmaceuticals, Serc by Unimend, Inc., and Triazure by

Calbiochem and Parke, Davis & Co. were withdrawn from the national market, withdrawn from clinical trials, or prevented from commencing clinical trials by FDA refusal to accept an IND. Empowered by the federal government, the FDA has been imbued through court proceeding with the right to seize as well as recall products and to prosecute the individuals or corporations responsible for legal violations of FDA regulations.

The FDA approves many products successfully when the products meet FDA regulations; however, the time and money invested in the overall approval process makes the venture an adamantine undertaking. Current legislature, policies, and politics tend to hinder instead of facilitate the progression of products into and through clinical trials and onto the market. The money required for such a undertaking prevents many drugs from reaching the people who require them most and increases the overall cost to the consumer once the drug has met with approval and is marketed. The impact of prolonged clinical trials results in the delay of the distribution and sale of a possible cure for a disease or disorder. Many cries of outrage towards the sluggish approval process by the FDA for promising drugs to combat diseases such as AIDS and cancer have slightly decreased the duration of the overall process; but it still remains a very lengthy process. Decreasing this time, in turn, decreases the cost to the manufacturer and sponsor possibly resulting in lower costs to the consumer. The question, though, must be raised as to the impact of shortening the overall time of this process in reference to the safety and efficacy of these products; therefore, great difficulty arises when a monetary value must be placed upon personal safety. Ultimately, the people of the United States are the ones who are being

protected under these statutes, but they, too, are the ones who are suffering and dying from these diseases. A balance must be wrought with the protection of the consumer and all of society as the foremost concern.

This Interactive Qualifying Project (IQP) will set forth guidelines and offer advice as to how companies can increase the success rates for their products during clinical trials with the aim of attaining and maintaining FDA approval. Advice concerning validation considerations throughout the entire approval process and beyond will be addressed with special attention to current GMP's and software/control system validation. The societal and economic impact of the entire regulatory affair will be examined with the aforementioned pharmaceuticals in mind and integrating the effects of improved approval success rates. This project was developed through individual interviews, archival research, and personal experience with VTS, Inc. It will partially fulfill Worcester Polytechnic Institute's (WPI's) undergraduate degree requirement of successful participation in an IQP that examines the regulation of interactions between pharmaceutical as well as medical technology and society.

2. THE HISTORY AND LEGISLATION OF THE FDA - A NEED FOR CONSUMER PROTECTION

Since the times of the Egyptian empire, ancient Greece and Rome, the necessity for laws protecting the public against the adulteration of food and medicines has been recognized (Patrick, 1988). This recognition was slow to dawn upon the US government throughout the 19th century because of few publicized incidents of poisonings and prevalent laissez-faire attitude of the government towards commerce. Not until the outrage of the public was spurred on by the words of Sinclair's The Jungle did Congress act. Urged by President Theodore Roosevelt, Congress voted in the Pure Food and Drug Act on June 30, 1906. This law stated that the adulteration or mislabeling of any food or drug sold between states would be considered a federal crime and fell under the jurisdiction of the Bureau of Chemistry, a branch of the Department of Agriculture. The Bureau of Chemistry would later become the Food and Drug Administration.

For over thirty years, Dr. Harvey Wiley, a leading chemist in the Department of Agriculture was a proponent of strict pure food and drug legislation; however, both government and commerce quelled his voice. When in 1906 he was appointed chief administrator in charge of enforcing the newly passed Pure Food and Drug Act, Wiley quickly organized a task force of young scientists to combat the overwhelming number of products that had to be analyzed and verified to be safe. Included within this task force was Walter Campbell, a lawyer who was able to define in legal terms the appropriate procedure and bureaucratic paperwork that needed to be completed for the organization to effectively function. Unfortunately, Wiley at the behest of President Theodore

Roosevelt resigned as head of this task force because of the many enemies he quickly made in agriculture, industry and government. The largest contributor to his forced resignation was his staunch support of a revision to the act, in which his task force would be granted policing power of these industries. Many in the government feared delegating such power to an organization and were under the assumption that it violated individual state's rights. His resignation would plateau the advancement of the organization for almost ten years during which time the rate of adulteration of products dramatically increased because of the increase in interstate commerce and overall productivity.

In 1924, ten years after Wiley's resignation, Walter Campbell was commissioned to head the established task force and all regulatory affairs. With the help of another book Your Money's Worth. A Study in the Waste of the Consumer's Dollar authored by Stuart Chase and F.J. Schlink in 1927, Wiley convinced Congress to create the Food, Drug and Insecticide Administration (FDIA) as a law enforcement agency with a need based budget provided by the Department of Agriculture and Congress, itself (Patrick, 1988). Chase and Schlink's work highlighted the fraudulent nature of many cosmetics, drugs, and foods. For example, in one case, tetrachloride was marketed as a grease dissolver, insecticide, and bath salt (Chase, 1927). The agency was commissioned in 1931 as the Food and Drug Administration (FDA), and Campbell was elected as its first commissioner. Following in the steps of Wiley, Campbell with the support of the entire FDA and newly elected President Franklin Roosevelt proposed a complete revamping of the original Pure Food and Drug Act of 1906. Tragedy would be needed to end this heated debate in Congress, and in 1937, 107 children died in the United States from a

purported strep throat medicine, Elixir of Sulfanilamide, which contained diethylene glycol (antifreeze). This horrible tragedy with the outrage of the public behind it forced Congress and the president to enact the Federal Food, Drug, and Cosmetic (FDC) Act on June 25, 1938. This act contained many major provisions including:

1. Provided authorization for corporate inspections
2. Required corporations to prove that their products were safe
3. Demanded the establishment of maximum dose efficiencies and safeties
4. Granted the FDA to pursue court orders against non-conforming corporations and their products
5. Allowed the FDA to prevent the marketing of products even if the product was fraudulent
6. Dictated that all products must be labeled with appropriate directions, dosages and cautions
7. Expanded the scope of the FDA jurisdiction to include medical devices and cosmetics (Hitchings, 1982).

In addition to the FDC Act of 1938, Congress also passed the Orphan Drug Act of 1938. This act had long lasting effects because it set forth tax credits and exclusive seven-year marketing rights to companies that persue treatments or cures for rare diseases. These benefits were offered as incentives for companies to expend money and resources in developing drugs that have sales, which may not recuperate their development costs. This act would have impacts on the early development of AZT for AIDS as well as many cystic fibrosis drugs used today.

In 1944, Paul Dunbar succeeded Commissioner Campbell as the commissioner of the FDA. In 1949 after recruiting US Representatives Frank Keefe of Wisconsin and James Delaney of New York, Dunbar persued the introduction of revisions to the FDC Act of 1938. Three amendments were passed over the next ten years that expanded the FDA control on food, drugs, and cosmetics; these amendments were: the Miller Pesticide Amendment of 1954, the Food Additives Amendment of 1958, and the Color Additive Amendment of 1960. The most important provision of these amendments arose out of the last two amendments as the Delaney Clause. This clause forbade the addition of any food, drug, or cosmetic additive or ingredient that had been demonstrated to be carcinogenic in laboratory animals. A European tragedy, coupled with staunch FDA opposition, led to the Kefauver-Harris Drug Amendments of 1962. In Europe, the drug thalidomide was prescribed first as a sedative for women in the later stages of pregnancy and later as relief for morning sickness at the onset of pregnancy throughout the 1950's. An American pharmaceutical corporation attempted to gain approval by the FDA to produce thalidomide and release it upon the US public; however, the FDA staunchly opposed the approval of thalidomide in the US. The FDA had saved numerous babies when two years later it was proven and published that thalidomide had induced horrible birth defects in the offspring of the pregnant women. This averted US tragedy prompted Congress to pass the Kefauver-Harris Drug Amendments. These amendments required that pharmaceuticals and medical devices must be proven to be effective and safe prior to their release upon the public and their manufacturers must report all adverse effects of their products. All of the amendments established the basis for the establishment of the

Good Manufacturing Practices (GMP's) to ensure that pharmaceuticals are safe, pure, and effective.

In 1959, Canada created the first GMP's that regulated the manufacturing and marketing of pharmaceuticals. The US quickly adopted GMP's with similar requirements dealing with personnel, documentation, and procedures necessary to ensure the effectiveness, purity and safety of all medical and drug products regulated by the FDA (Lubiniecki, 1994). Also occurring during the 1970's, the Medical Device Amendments of 1976 were passed to completely encompass all devices used in the health care profession, such as contraceptives and stethoscopes, as under the jurisdiction of the FDA. In 1978, the FDA proposed extensive revisions of the GMP's and allowed the pharmaceutical industry to review and comment upon the regulations. Those comments as well as the FDA Commissioner's responses were addressed in the Preamble that preceded the publication of the final GMP's. Finally, in 1983, Congress passed the Anti-Tampering Act to require manufacturers to place their products in tamper-proof packaging and outlawed the tampering of packaged products. Printed in the Code of Federal Regulations 21, the GMP's are routinely revised with updated regulations and requirements in an attempt to stay abreast to the rapidly changing pharmaceutical and biotechnological industries, and the FDA attempts to advise Congress with up-to-date information for the creation of new and more effective legislature on all of these products.

The eight branches of the administration service every facet of the needs of the FDA from public relations to testifying before Congressional committees to evaluating products for approval (*Figure 1*). Six agency centers for research and development have been established to explore the problems faced by the drug industry and to investigate new methods for producing and packaging pharmaceuticals. Twenty-one district field offices operate under the control of the Office of Regulatory Affairs. These twenty-one offices conduct all FDA audits for the companies and supervisory duties for the FDA in their specified regions, enforce all FDA policies for these corporations, and address public issues. The FDA employs a vast array of scientists, lawyers, and validation engineers who make up the majority of the staffs at these district offices; without them and the cooperation of the companies within their jurisdiction, the FDA would be unable to function successfully. With the support of the US Supreme Court, the FDA has interwoven itself with the community at large and the US Congress. The safety of all drugs and medical devices within the US is now the complete responsibility of the FDA to such a degree where the consumer does not question whether this product is safe but relies upon it to be so.

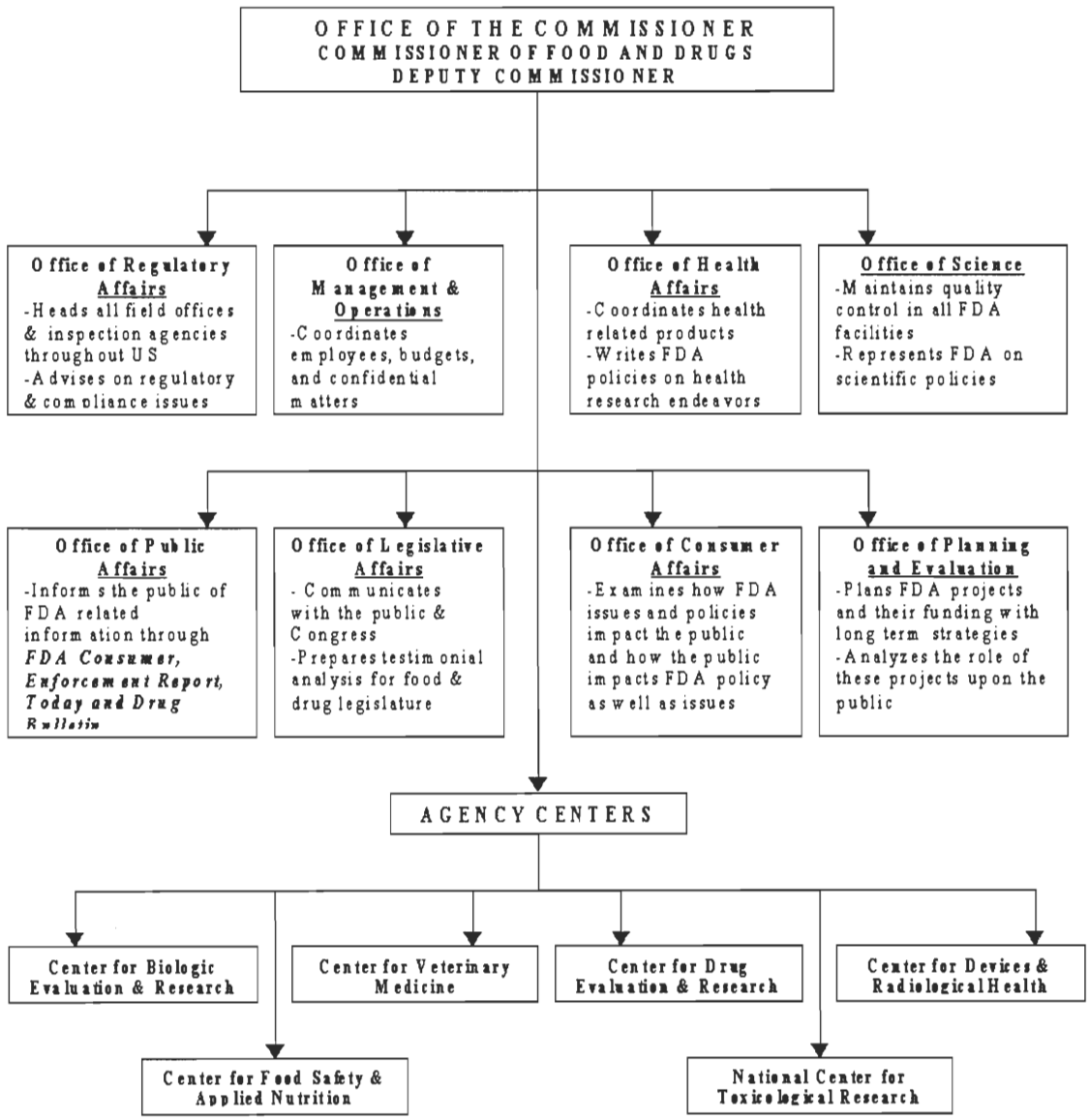

Figure 1. The departmental office breakdown of the US Food and Drug Administration, a branch of the Department of Health and Human Services, and its centers of research and development (Patrick, 1988).

3. THE FDA REGULATION OF PRODUCTS

In the Federal Register on June 20, 1963, the FDA specified the first good manufacturing practice (GMP) in US history. Prior to the passage of the first US GMP, Canada had established national drug manufacturing standards of practice from which the US derived the initial GMP's. As technology and knowledge advanced, the GMP's had to evolve in an never-ending battle to protect the consumer against unsafe, impure, and ineffective drug products. Today, current GMP's (cGMP's) are issued by the Commissioner of the FDA in the Code of Federal Regulations (CFR's) and carry the force of law. These cGMP's have diverged and been accepted in other areas of pharmaceutical research, development, testing and production. Good Clinical Practices (GCP's) and Good Laboratory Practices (GLP's) have been established to set forth standards of acceptability by the FDA. For companies to gain approval of their initial Investigational New Drug Application (IND) and their final New Drug Application (NDA) by the FDA, company practices, procedures, equipment, and product are required to meet current GLP, GCP, and GMP regulations where applicable. As the crucial first step in FDA approval of an IND, meeting cGMP as well as cGCP requirements is foremost in the aims of quality control, quality assurance, and validation departments of drug and medical device corporations. Because of the overwhelming importance of cGMP's, a basic understanding of these regulations is necessary for anyone examining FDA approval and consumer protection.

The minimum current Good Manufacturing Practices for Finished Pharmaceuticals and Medical Devices are promulgated in Chapter 21 Code of Federal

Regulations, Parts 211 and 820. cGMP's specify the minimum essential criteria that must be met prior to pursuit of an IND. The GMP's can be broken down into the base ingredients of any company: departments, personnel, facility, equipment, testing, packaging, and marketing. The FDA outlines the regulations applying to the departments that must be established, the personnel that must be hired, the equipment that is used in production, the packaging in which the product will be marketed, and the testing to which the product must be subjected post-production. A Quality Control (QC) department must be established to oversee product and department compliance to the cGMP's as well as to all other applicable government statutes. QC maintains control of the facility in relation to ensuring of quality compliance. QC establishes all written Standard Operating Procedures (SOP's) for all aspects of the company from equipment operation to laboratory testing to personnel training. Hired personnel must meet the requirements of their job description and undergo appropriate training including cGMP training. With consideration given to the Occupational Safety and Health Act (OSHA) requirements, personal hygiene, health and safety are detrimental to achieving and maintaining FDA and OSHA approval. The design and construction of a manufacturing and/or packaging facility must facilitate the sanitary production and/or packaging of the drug or medical device. The facility must be amenable to safe working conditions with adequate lighting, ventilation, and environmental conditions for all personnel. Sterile drug production cleanrooms are classified by the number and size of the particulates within the air. These cleanroom classifications must be maintained with an appropriate air filtering system supplied by a Heating, Ventilation, and Air Conditioning (HVAC) system monitored by a

control system. *Tables Ia* and *Ib* represent the means of room testing for classification determination via particle count and the acceptable limits for those clean rooms. The

TABLE Ia. MINIMUM NUMBER OF SAMPLING POINTS REQUIRED FOR VERIFYING THE CLASS OF A CLEAN ROOM ACCORDING TO FEDERAL STANDARD 209E (1992)

Area of Clean Room (ft^2)	Class		
	100	10,000	100,000
100	4	2	2
200	8	2	2
400	16	4	2
1000	40	10	3
2000	80	20	6
4000	160	40	13
10,000	400	100	32

TABLE Ib. ACCEPTABLE PARTICLE SIZE PER SAMPLE ACCORDING TO INTERNATIONAL ORGANIZATION FOR STANDARDIZATION ISO-14644-1 (1998)

Room Classification	# of Particles of Size 0.1 µm per Cubic Meter
100	100
10,000	10,000
100,000	100,000

equipment used in all facets of drug production must be validated to ensure proper installation, operation, and performance; these tests verify the proper working order of the equipment while determining that all in-process equipment and materials (ie equipment lubricants, coolants, cleaning agents, etc.) do not adversely impact the final product. Computer controlled and electronic equipment must be calibrated annually and tested through validation exercises for assurance of proper execution of all formulations

and actions, correct input and output wiring, and exact information transfer of data. Lot testing of final product must routinely occur to ensure and document the sterility, activity, quality, and safety of the pharmaceutical. This routine testing also verifies the process and product stability through comparison to in-place standards of reference that have been proven as scientifically sound. Finally, the packaging and labeling of the product for market release must be strictly controlled and include quantity, ingredients, dosage, directions, warnings, and expiration dates. As a result of the 1982 poisonings by cyanide laced Extra-Strength Tylenol, the FDA was prompted to require that all product packaging be tamper resistant. cGMP's establish the basic regulatory standards that must in place for all aspects of a corporation prior to and following IND and NDA acceptance.

The current Good Clinical Practices (cGCP's) have been standardized by the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. The countries of the European Union (EU), Japan, Canada, Australia, the United States , and the World Health Organization (WHO) consolidated and unified GCP's. cGCP's are applicable to the testing of IND approved products upon human subjects during clinical trials for NDA acceptance. These practices are the moral, scientific, and ethical standards that must be met in the formulation and execution of clinical trials involving humans as subjects. Occurring concurrently with IND submission, the first step in the clinical trial process is the establishment of an Investigator's Brochure (IB) outlining the drug to be tested in trial, the procedures for those tests, numbers of subjects in placebo and test samples, and the means for blind analysis of data. The Sponsor organizes the trial including the

appropriate SOP's, monitoring, record keeping, documentation that GMP requirements were met in production, and allocation of duties during the trial. The proposed study with the IB must be reviewed and approved by an established Investigator's Review Board (IRB) or Independent Ethics Committee (IEC) that is not affiliated directly with the drug manufacturer (Sponsor) but may be affiliated with the Investigator. Trial subjects must be provided with written informed consent forms and told of true nature of the drug whether placebo or not at the completion of the study. The content of these consent forms is controlled and dictated by the IRB or IEC. During the trials, the Investigators should follow randomization procedures to ensure untainted results. Progress reports and summaries of the studies must be submitted documenting the status of the trials to the board or more regularly, if so specified by the board. The final statistical analysis of data and the concluding summaries of the investigation are reviewed and approved by the Board. The Sponsor is interwoven throughout this process on both the investigation and review sides of all collected data. The cGCP's maintain a uniformity in the establishment of necessary guidelines, appropriate procedures, and structure of clinical trial investigations to produce an objective, universal, and safe study.

4. STARTING-UP - THE ROAD TO CLINICAL TRIALS

First introduced in 1963, the cGMP regulations were authored with a subjective interpretation in mind that would allow the FDA and manufacturers to interpret the applicability and detailed specifications on a per product basis. Many pharmaceutical and biotechnology corporations are critical of the lack of detailed specifics in these regulations; however, flexible language is necessitated if the FDA is to regulate the vast variety of pharmaceutical and products that are under its jurisdiction. Outside validation consulting firms are currently hired by companies that are under the jurisdiction of the FDA. These consulting firms specialize in the validation and regulatory requirements of the pharmaceutical, biotechnology, solid dosage, and medical devices industry by the FDA.

The first use of the word validation in terms of regulatory affairs was included in the proposed 1976 revisions of part 211.113 (b) in the CFR 21; it was formally accepted in 1978 dawning the age of validation, quality control, and quality assurance (Goves, 1987). Today, validation firms are plentiful and well experienced in numerous pharmaceutical manufacturing processes (sterile and non-sterile), automated computer control systems, laboratory and information systems, as well as medical devices manufacturing. Because the federal and international regulations governing the manufacture of bulk solutions and sterile drugs, biotechnology processes or the manufacturing of medical devices are both growing and changing at an increasing rate, experts in the validation field must keep abreast of the regulations. Their sole purpose is

aiding companies in attaining the status of clinical trials and to ensure FDA approval of facilities and products.

One very prominent issue currently is the use of computer controlled systems in running the manufacture of products, in assaying test samples, and maintenance as well as monitoring of the production facility. These intricate control systems rely upon programmable software both canned and custom, purchased or written by the company. "Software validation has become one of the most critical issues to be addressed by the FDA concerning correct product labeling, dosage, and manufacture in the last decade" (Ghayour, 1999). The following section details the importance and requirements of software and hardware system testing. The necessary documentation to be completed prior to commencement of manufacture is specified. This section is a useful guideline for corporations and manufacturers starting down the road to clinical trials and beyond.

4.1 Software and Hardware System Validation

The following definitions have been extracted from multiple sources to provide assistance to the reader in better understanding the guidelines set forth. These definitions may change over time, and the reader is advised to consult the reference sources to obtain the most current definitions.

Acceptance Testing: Formal testing conducted to determine whether or not a system satisfies its acceptance criteria and to aid the manufacturer in the determination of whether or not to accept the system (IEEE).

Boundary Value Testing: A testing technique using input values at, just below, and just above the defined limits of an input domain; and with input values

causing outputs to be at, just below, and just above the defined limits of an output domain.

Branch: (1) A computer program construct in which one of two or more alternative sets of program statements is selected for execution. (2) A point in a computer program at which one of two or more alternative sets of program statements is selected for execution. (3) Any of the alternative sets of program statements in (1). (4) The performance of the selection in (1) (IEEE).

Branch Testing: Testing designed to execute each outcome of a decision point in a computer program (IEEE).

Component: One of the parts that make up a system. A component may be hardware or software and may be subdivided into other components. The term "module," "component" and "unit" are often used interchangeably or defined as sub-elements of one another. The relationship of these terms is not yet standardized (IEEE).

Factory Acceptance Test (FAT): Testing activities conducted at the vendor/supplier facility. The FAT may include any combination of unit, integration, or system.

Functional (black-box) Testing: Testing that ignores the internal mechanisms of the system software or a software component and focuses solely upon the outputs generated in response to selected inputs and execution conditions. Testing conducted to evaluate the compliance of the system with specified functional requirements.

Installation Qualification (IQ): Documented verification that all key aspects of the installation adhere to approved design intentions according to system specifications, and that the manufacturer's recommendations have been suitably considered. Appendix II contains a sample draft IQ.

Integration Testing: Testing in which software components, hardware components, or both are combined and tested to evaluate the interaction between them (IEEE).

Interface Testing: Tests conducted to evaluate whether systems or components pass data to one another and control correctly (IEEE).

Nonconformance: A variance between an actual event or result and a planned or expected event or result. It is also know as an incident.

Operational Qualification (OQ): Documented verification that each unit or subsystem operates as intended throughout its anticipated operating range.

Included within this protocol are environmental, user load, and coexistence with other products verifications. Appendix III contains a sample draft OQ.

Path: In software engineering, a sequence of instructions that may be performed in the execution of a computer program.

Path Testing: Testing designed to execute all or selected paths through a computer program (IEEE).

Performance Qualification (PQ): Documented verification that each unit or subsystem performs as intended over an extended period of time, usually one year.

Regression Testing: Selective retesting of a system or component to verify that modifications have not caused unintended effects and that the system or component still complies with its specified requirements (IEEE).

Site Acceptance Test (SAT): Testing activities conducted at the installed production site. The SAT may include any combination of unit, integration, or system testing.

Statement: In a programming language, a meaningful expression that defines data, specifies program actions, or directs the assembler or compiler (IEEE).

Statement Testing: Tests designed to execute each statement of a computer program (IEEE).

Stress Testing: Tests conducted to evaluate a system or component at or beyond the limits of its specified requirements (IEEE).

Structural (white-box) Testing: Examining the internal structure of the source code. It includes low level and high level code review, path analysis, auditing of programming procedures and standards actually used, inspection for extraneous "dead code," boundary analysis and other techniques. Requires specific computer science and programming expertise (Merck CCR Lexicon). It is testing that takes into account the internal mechanism of a system or component. Types include branch testing, path testing, and statement testing (IEEE).

Test Specification: A document that specifies the detailed instructions for the set-up, execution, and evaluation of results for a given test case. This document includes specifications for the test inputs, execution conditions, and predicted results (IEEE).

Test Unit: A set of one or more computer program modules together with the associated control data (for example, tables), usage procedures, and operating procedures that satisfy the following conditions: (1) All modules are from a single computer program; (2) At least one of the new or changed modules in the set has not completed the unit test; and (3) The set of modules together with its associated data and procedures are the sole object of a testing process (IEEE).

Unit (or Component) Testing: Testing of individual hardware or software units or groups of related units (IEEE).

Design Phase

Preparation of User Requirements Specification

The User Requirements Specification (URS) describes the specification from the user's perspective. It describes "WHAT" the completed system is to do and provides the basis for the design, and provides the basis for evaluating the system against "written specifications" for validation. The URS should be described in terms familiar to the user and reflect the business needs based on the analysis of requirements stated by the user. The URS serves as the agreement between the developer (author of the URS) and the user. Therefore the URS must be approved by the developer, user, and the QA. The URS should become a controlled document. If the scope is changed at any point, the document must be amended with user concurrence. This document should be sufficiently detailed to allow System Design Specification to be derived from this.

Preparation of System Design Specification

The System Design Specification (SDS) describes the system from the system developer's point of view. The SDS will describe "HOW" the URS will be met. It

provides technical details about how the URS will be met. The SDS describes how the system is to be implemented by providing sufficient detail to construct the system software, build and/or purchase the system hardware and support devices. Further, it is the basis for modular and subsystem development, test planning, subsequent maintenance and enhancement. The SDS should become a controlled document. If the scope is changed at any point, the document must be amended. The SDS must be defined and approved by the developer, user and the QA. Written approval is required to proceed with construction/development.

Design Reviews

Numerous project meetings involving all project team members, including but not limited to, system developers (in-house or external), QA personnel, users, etc. shall be maintained to review the design and functional requirements for the software product. Results should be maintained. The project team members should review findings and recommended action plans, and resolutions are required. All design documents should be updated and controlled.

Development Phase

Develop Hardware

The developed system hardware should completely address all hardware elements in accordance with the URS and SDS. All stages of hardware development should be in

conformance to applicable Standard Operating Procedures (SOP's) as it applies to change control and documentation version control.

Develop Software

Perform Development and Physical Audits

In-process hardware and software development, audits should commence subsequent to design completion. Audits will assure compliance with technical standards, specifications and procedures for development and will focus on appropriate phases for:

- Design
- Development
- Testing

Physical audits should be conducted to inspect and ensure the completeness of project deliverables and documentation for system support and developed software products. Audit reports will be issued to the appropriate management groups. Audit findings and the management personnel review recommended action plans should, and resolution must be required.

Types of Testing

Various types of testing are conducted during the phases of a system life cycle; however, all types of testing contain the same basic elements: an item that it tested (e.g. a unit, a program, a subsystem, a system, etc.), a method or procedure by which an

apparatus or environment in which the test method is conducted, and a standard against which the test result is measured for acceptance. Any well-engineered quality computer-related product is subjected to the various types of testing during its development and implementation. The key variable is where responsibility lies for each type of testing. These responsibilities should be clearly defined in the system Automation Quality Assurance Plan. All types of testing are planned and documented activities and therefore should be conducted according to pre-approved protocols or test specifications and under change control procedures.

Software Development Testing

During the development process, two basic forms of testing occur: structural and functional testing. These two forms of testing are primarily performed during the construction phase of the system life cycle and prior to installation of the system into the production environment; however, exceptions may occur to this rule. For example, when the application is being installed into a new hardware platform, development testing may be performed on the hardware system that will actually become the production environment. When development testing is performed in this manner, the testing must be completed in a controlled fashion that ensures that the system remains unreleased for general usage.

Software Structural Testing

Structural testing is a testing that takes into account the internal mechanism, structure, and logic of a system or component (unit). It challenges the test unit's detailed design and source code. Two basic method of executing structural testing exist: static and dynamic analysis.

Static Analysis

Static analysis is the process of evaluating a system or component based on its form, structure, content, or documentation. It is, also, known as structural verification and includes detailed examination and analysis of the source code and its logic. Static analysis may be performed through manual or automated methods.

Manual methods may include code inspections, code walk-throughs, audits and reviews. Code inspections are performed to verify that the source code adheres to the software development and coding standards (e.g. language standard, naming conventions, commenting conventions, complexity constraints, style, etc.). Walk-throughs are performed to manually exercise the logic of the source code, to verify that the functional logic satisfies the software requirements and specifications, and to detect logic errors that may be transparent to the computer. Manual methods are more easily performed on smaller units or modules of source code because of the time consuming and pain-stakingly intricate

complexity of larger units. Automated methods utilize software tools that analyze the source code for syntax error, complexity measures, etc.

Static analysis methods should be execute by personnel who are appropriately qualified for the software technologies being utilized. The results of static analysis should be documented in a manner that will identify the test unit that was inspected, the items that were verified, the date of verification, and the results of the static analysis.

Dynamic Analysis

Dynamic analysis is the process of evaluating a system or component (unit) based upon its behavior during execution. It challenges the functional behavior of the logic and the decisions, paths, and branches that are made by the software. Although dynamic analysis is challenging the functional behavior of the software, it is doing it at a level that requires an understanding of the internal mechanisms, structure, and logic of the software. For example, a software function may perform a mathematical algorithm. During functional testing, the input data are the values 2 and 2, and the expected output is 4. The execution of the functional test, with the input values of 2 and 2, yields the expected results of 4, and the test condition passes. There is no indication if the algorithm was N+N, N*N, or N squared. This algorithm can only be determined and tested during

the structural testing of that software function and requires an understanding of the source code algorithm.

At the completion of executing all of the forms of dynamic analysis, all of the application software source code that was identified for testing has been executed. It should be apparent that the actual application software source code is required to conduct full dynamic analysis. Sometimes, additional software tools such as test harnesses, driver programs, test data generators, input and output simulators, stubs, etc. may also be required to isolate portions of the application software source code, set test values or variables, and determine as well as capture the behavior of the executed software, and this fact is not always obvious.

Some general types of test conditions may be exercised during the various forms of dynamic testing. Consideration should be given to the applicability of these test conditions when developing the test specifications for the unit, integration, and system testing. For example, boundary testing may be applicable to both boundary values within a unit and boundary values between integrated modules or components. These general types of testing conditions are as follows:

Boundary Conditions: A boundary value is a data value that corresponds to a minimum or maximum input, internal, or output value specified for a system or component. Boundary testing is a technique that employs input values at, just below, and just above the defined limits of input and output domains. Boundary testing may be applicable at the unit, integration, or system levels of testing.

Branch Conditions: A branch is a decision point where one of two or more alternative paths may be taken, as stated in its definition. Branch testing is designed to execute each outcome of a decision point, or branch, in a computer program.

Path Conditions: A path is a sequence of instructions that may be performed in the execution of a computer program. Path testing is designed to execute all or selected paths through a computer.

Statement Conditions: A program statement is a meaningful expression that defines data, specific program actions, or directs the assembler or compiler. Statement testing is designed so that every statement of a computer program is executed at least once.

Stress Conditions: Stress tests are conducted to evaluate a system or component at or beyond the limits of its specified requirements. Many specified requirements can be stress tested. A boundary value requirement can be stress tested beyond the limits of its specification (worst case testing). A capacity requirement for memory, network traffic, or device inputs must be stress tested beyond the specified normal limits; therefore, stress testing is applicable at the unit, integration, or system levels of testing.

Valid/Invalid Input Conditions: Testing of valid input data utilizes input that is an acceptable specified value or within an acceptable specified range of value. Conversely, testing of invalid input data utilizes input that is not an acceptable specified value or is outside an acceptable range of values.

Software Unit Testing

The primary objective of unit testing is to attempt to cause failures in order to detect errors in the software unit. The unit test should exercise: the unit's defined states (inactive, active, awaiting a message, or active processing of a message); handling of valid and invalid input; algorithms or internal data structures; and the decision boundaries of the unit's control logic. Testing entails the measurement of behavior against a documented specification. Since Requirements Specification

documentation may not be detailed enough for effective unit testing, Design Specification documentation is often required. A combination of unit requirements, design, and implementation information may be needed to adequately specify the unit's required behavior. This testing is essential in establishing the baseline against which the actual behavior of the unit will be compared.

Since unit testing is performed on manageable, discrete units of software, it is the recommended level of testing during which boundary, branch, path, and statement testing are conducted. This process will ensure that all statements in the unit have been successfully executed at once. Based upon the criticality of the unit, an automated tool may be utilized that can provide a summary code coverage during test execution. The tools indicate the amount of source code executed and may also identify unexecuted branches.

Software Integration Testing

Software integration testing is the process of testing the combined software components to evaluate the interaction between them. It examines the transfer of data and control across the component interfaces. During development, software integration testing is performed before the application software system is integrated and tested with any external hardware equipment or devices. Prior to execution or software integration

testing, the integration sequence of the software units must be identified, and the interfaces between the unit must be specified. These specifications will require an understanding of the logic structures outputting data from the unit, passing control based on logic branches, formatting data and messages, etc. Software integration testing should not be confused with the system level integration testing that occurs when the application software system is integrated with other systems or equipment and devices.

Software System Testing

Software system level testing is considered a form of structural testing since it requires an understanding of the underlying logic for handling system level interfaces and functions. Since software system testing is performed before the application software system is integrated and tested with any external hardware equipment or devices, input and/or output simulation of external equipment, device, or external systems must be provided. Software system testing may include, but is not limited to, the following:

- Testing of user interfaces that may not have been easily tested at the unit or integration level tests
- Data flow testing
- Stress testing which may include tools to simulate the following:
    - peak volumes of data
    - high rates of data input (sustained or repetitive)
    - maximum number of users
    - excessive numbers of inputs (devices)
    - maximum memory requirements
    - unexpected sequences of inputs and operations

    - unexpected timing of inputs and operations
    - power failures
- Security testing which may be based on screen, field level or data level internal logical constructs.
- Testing of memory requirements during various load conditions.
- Exercising file of database contention conditions.
- Evaluating the behavior of the system when the following occur:
    - file or database full conditions
    - system crash or failure while a transaction is in process
- Error handling.
- Evaluation of total system resource utilization.

Functional testing challenges the software system's external requirements and Design Specifications. It is concerned with inputs and outputs to functional system units and not with how the output is generated. This functional testing is basically a preliminary testing of those items that will be tested during user acceptance testing.

In the case of certain externally developed software, this testing may be performed at the vendor site with the application software system combined with hardware or devices. This is called a Factory Acceptance Test (FAT). The completion of a FAT may result in acceptance of the system for installation at the Pall target site. Cases also exist where another form of software/system testing is performed after the system is installed at the Pall target site. This is called Site Acceptance Testing (SAT). Both FAT and SAT may vary in depth of testing that is conducted and may include any range of unit, integration, system and functional testing. Neither FAT nor SAT are considered full replacements for production system acceptance testing which is performed after production

installation qualification and operational qualification. However, thorough documented testing during software functional testing, FAT, or SAT may decrease the required depth and extent of testing during the production system acceptance testing.

Software functional testing may include, but not be limited to, the following:

- Normal inputs
- Unexpected inputs
- Limits or boundaries of inputs and outputs
- Special cases (0, null, empty strings, leap year, year 2000)
- 'Worse case' conditions
- Performance testing of:
    - response times
    - data throughput capacities
    - transaction loads
    - continuous use
- Volume testing
- Security testing
- Recovery testing
- Usability testing (operator usability e.g. respond to alarms)
- Compatibility testing (one application to another external system, to networks)
- System backup and restoration

Hardware Development Testing

Hardware testing is designed to ensure that the hardware environment, defined by the User Requirements Specification and System Design Specifications, has been properly established prior to software installation. Typically this testing takes two basic forms: inspections, and continuity checks.

4.2 Clinical Trials – A Result of an Approved IND

The FDA approves an Investigational New Drug Application for a pharmaceutical to commence one or more phases of clinical trials to determine the affects of the drug upon human test subjects. IND's are carefully regulated by the FDA because of the human health risk involved in the study of previously untested drugs. Written by the drug Sponsor, an IND describes in detail the pharmacological, toxicological, and biological effects of the drug in previous animal or human studies of the drug or similar drugs. The chemical composition of the drug substance is examined both structurally and kinetically. The formulation and known clinical effects are critical in the FDA's evaluation of whether or not to approve a drug for investigation. The IND offers a general investigational plan about the goals and length of the investigational study to be conducted. Included within the IND is the Investigator's Brochure (IB) that details the investigational drug, the methods of testing, testing population numbers, and methods for statistically, quantitatively, and qualitatively analyzing the produced data. This IB is provided to both the Investigators and the established Investigator's Review Board (IRB) or Independent Ethics Committee (IEC); therefore, the members of the Board and the Investigators of the study are specified along with the institutions that will conduct the investigation within the IND. Specified within the IND, investigational studies protocols summarize the specific procedures for conducting investigations of the pharmaceutical under examination. This summary should include the number of patients within a study, the dose plan for evaluating a dose-response, the critical safety criteria of the

experiment, and the safety exclusion margin for patients (21 CFR Part 312, 1998). For Phase One testing, the investigational protocols are less detailed and structured to allow for more study variability integration. Because the drug, in many cases, has yet to be tested upon human subjects, the pharmacological and clinical effects may be difficult to assay and predict, especially in a dose-response study; therefore, a more loosely written protocol allows for the integration of unknown factors. Within the *Appendix I*, a Phase One Study Manual protocol has been attached for a sample of the information that must be contained within an investigational protocol. Phase Two and Three investigational protocols are much more stringent and detailed in procedural specifications and wording. These latter protocols are written with contingencies included for study deviation and unknowns. Following approval of the IND by the FDA, Investigators, and IRB or IEC, clinical trials may commence delving into the clinical effects of the drug upon patients.

The FDA has established three phases of investigation to evaluate the safety, effectiveness, and responses clinically within human subjects. These trials begin with a small population of test subjects, which progressively increases as the phase of the trial increases. Phase One clinical trials are normally the first time that the investigational new drug has been tested on human subjects. The main objective of a Phase One trial is the determination and documentation of the clinical effects of the drug upon the human body including the metabolic and physiologic effects on the subject. With this objective as the primary aim, both

sufferers and non-sufferers of the disease or disorder under investigation may be used as test subjects. Once these clinical effects have been determined, dose-response studies can be initiated, from which effectiveness results may be drawn, an ideal occurrence for Investigator and Sponsor. Other additional studies may be established during Phase One trials to examine in more depth the metabolic activity of the drug in the human body or the basis for the disease-drug-human interaction. Phase One test subject populations usually range from between 20 to 80 individuals (21 CFR Part 312.21, 1998). Phase One clinical trials establish the necessary foundation for the planning and execution of the expanded, future trials of Phase Two.

During clinical trials, the Sponsor is constantly revising and amending the IND with the new studies, procedures, and data; furthermore, annual reports, or more frequently when specified, must be submitted to the FDA detailing the status of the trial, any analyzed results in addition to any conclusions that can be drawn from those results. For the commencement of Phase Two trials, a revised IND must be submitted to the FDA for approval into the next phase of trials. Phase Two investigations entail controlled clinical studies of patients to ascertain the effectiveness of the investigational drug for a specified clinical symptom or symptoms of the disease or disorder under study. Usually, an investigation studies time-constrained side effects of the drug in humans. Phase Two test subject populations usually are less than a few hundred individuals who suffer from the disease or disorder under examination (21 CFR Part 312.21, 1998). The

duration of Phase Two trials is ordinarily longer than the Phase One studies and with more specific pharmacological effects under study with those effects observed during the Phase One trials more specifically focused upon. The control and limitations coupled to the demonstration of drug effectiveness during Phase Two trials provide further evidence in support of approval by the FDA of the Sponsors Phase Three IND.

Phase One and Two clinical trials provide the basis for Phase Three evaluations of the drug over long-term drug exposure in an extensive subject population. The FDA will approve an IND for Phase Three trials only after the Sponsor and Investigators have documented appropriately convincing preliminary evidence supporting the effectiveness and safety of the drug. Phase Three trials allow for uncontrolled studies of the drug to examine its clinical effectiveness in a vast population and its relative safety. From these studies, an evaluation of the benefit versus risk of the drug to the patient can be conducted to support FDA approval of the NDA. This final phase of trials provides the informational source of all drug and physician information packages. The Phase Three test subject populations range from between a few hundred to several thousand patients (21 CFR Part 312.21, 1998). Following completion of Phase Three clinical trials, the FDA reviews all collected data, summaries, and conclusions in the final IND, which coupled with separate Sponsor testing becomes the NDA, and the FDA makes its approval decision. If the drug is approved, the manufacturer can market and sell the drug throughout the country; however, if the NDA is denied approval,

the drug may be returned to any phase of clinical trials or removed completely from the accepted IND drug list dependent upon the results of the final trial.

4.3 NDA Acceptance – Maintenance of FDA Approval

The approval of a New Drug Application (NDA) is the ultimate goal of all clinical trial Sponsors because approval grants the Sponsor the ability to finally manufacture, market, and sell the drug product that has been tested rigorously through lengthy and costly clinical trials. As a document, the NDA opens with a summary of the entire drug application. This summary is oftentimes used as the Summary Basis of Approval, the public release hailing the approval of the investigated drug. The drug substance of the investigated drug is stated with a detailed drug production, testing, and packaging methodology as the manufacturing scheme for the drug. The drug products or ingredients of the pharmaceutical are also specified in the drug substance section. The pharmacological, biological and toxicological effects of the drug determined in the *in vitro*, animal, and human studies are documented. Collected throughout the entire clinical trial investigations, all clinical data must be submitted within the NDA. The NDA details the final stability runs on manufactured drug and analytical methods for data evaluation. The Sponsor submits three signed copies of this voluminous document to the FDA: an Archival copy, Review copy, and Field copy (21 CFR Part 314.50, 1998). The entire approval process is an expensive and long-term endeavor dictating private, federal, and public financial support from the time of discovery until the final approval of the NDA; approval

allows the manufacturer to finally capitalize on the arduous and often adamantine undertaking that commenced many years prior.

Unfortunately for the manufacturer, the approval story does not end at the time of NDA acceptance; the FDA requires the submittal of reports to update and ensure the FDA that a product maintains its purported safety, efficacy, and stability. During the distribution and sale of the drug product, incidents may be reported to physicians and manufacturers of "adverse drug experiences" (21 CFR Part 314.80, 1998). These experiences are events associated with clinically observable adverse effects during human usage of the drug whether as an overdose or not. Any serious, unexpected, or statistically continuous reaction must be reported to the FDA immediately. Manufacturers must submit NDA – Field Alert Reports if a lot or batch is found to be improperly labeled or adulterated in any way. The FDA will publish these alert reports as well as a recall request if the product has been released. Annual reports must be submitted to the FDA including a product summary similar to the NDA summary, marketing as well as shipping data, changes in the manufacturing scheme under change control SOP's, clinical and non-clinical data, variations in drug compositions under change control SOP's, and status reports on any conducted post-marketing investigations (21 CFR Part 314.81, 1998). Finally, all advertising and promotional materials must be submitted to the FDA for approval to ensure that the message portrayed is truthful and accurate. The FDA maintains a constant

vigil over even approved drug and pharmaceuticals on the market to guarantee consumer protection against unsafe, mislabeled and impure products.

5. FDA APPROVAL SUCCESS STORIES

5.1 The Story of Erythropoietin – EPOGEN (EPO) by Amgen, Inc.

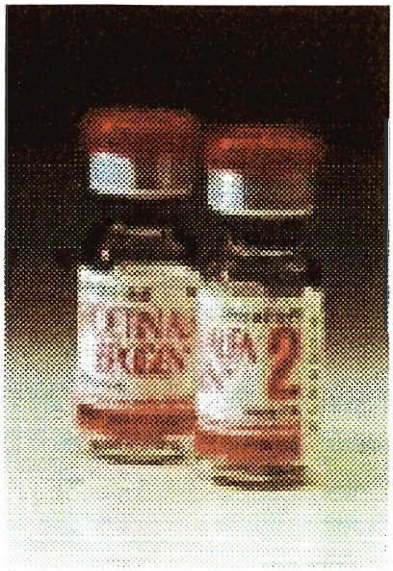

Figure 2. EPOGEN® (Epoetin alfa) manufactured and distributed by Amgen, Inc., of Thousand Oaks, CA.

Normally in humans, the hormone erythropoietin (EPO) is secreted by the kidney to regulate the manufacture of red blood cells. Red blood cells are essential for the transport of oxygen to cells throughout the body and thus the amount of energy available to those cells. Kidney failure is often coupled with a loss of ability to produce EPO. In the past, chronic renal failure was fatal because the kidney slowly loses its ability to function; however, with the invention of dialysis, sufferers were able to live much longer lives but with a low quality of fatigued life and at substantial costs. Renal disease is usually accompanied by severe anemia as a result of decreased or halted EPO manufacture. This anemia is the cause for the fatigue because the sufferer has a drastically lowered red blood cell count. Treatment of anemia has always been expensive, time-consuming, and highly unsuccessful. These treatments included frequent blood transfusions or

injection of the male androgen hormone, which would induce for a short time red blood cell production. These treatments risked major infectious and immunological side effects. Androgen treated patients began to develop secondary male sex characteristics (P*h*RMA, 1995). Amgen, Inc. of Thousand Oaks, California, was the first to clone the human genetic sequence for erythropoietin and produce recombinant EPO *in vitro* in 1983, which has ended renal failure anemia in many patients restoring their daily lives.

The research team lead at Amgen, Dr. Fu-Kuen Lin was responsible for the novel approach of using a gene library to probe the human genome to identify the gene for EPO. His success in isolating and purifying the EPO gene was only the first step for Amgen in obtaining approval for such a novel biotechnology drug. Chinese Hamster Ovary (CHO) mammalian cells were chosen as the host cells to produce EPO; however, the use of recombinant DNA technology, at this time, was still a very novel field and heavily regulated by the FDA because of its novelty. Amgen thus had to develop methods of analysis and dramatic preclinical studies of dose-responsiveness in animals to demonstrate the efficacy and safety of recombinant EPO (P*h*RMA, 1995). After three years, in the spring of 1985, Amgen pursued the IND approval for the commencement of Phase One clinical trials.

At this time, Amgen was a company limited by resources, funding, and credibility, which hampered clinical trials and NDA approval for over three years.

Fortunately, the safety of EPOGEN (Epoetin alfa) was rapidly established during Phase One trials. Eleven centers of Investigation were assembled for Phase two and Three trials. The efficacy of the drug was dramatically shown in a selected group of patients who were selected for a doubled dose of EPOGEN. This dosage demonstrated very high increase in red blood cell count and maintained the safety of the drug.

> "Amgen was often very close to pulling the plug on EPO clinical trials because of the enormous costs to a company with limited resources…However, the constant successes of the product ensured its survival and continued funding" (Kaye, 1999).

For two years time and with unrelenting dedication and vast expenses, Amgen produced an NDA for submission to the FDA. This submission was approved in June of 1989 allowing Amgen to manufacture and sell EPOGEN in the United States for the treatment of anemia associated with renal failure. EPOGEN has become the drug that Amgen has based much of its success upon and has allowed Amgen to become one of the world's largest and most successful biotechnology companies.

5.2 The Story of Enalapril Maleate– Vasotec by Merck & Co., Inc.

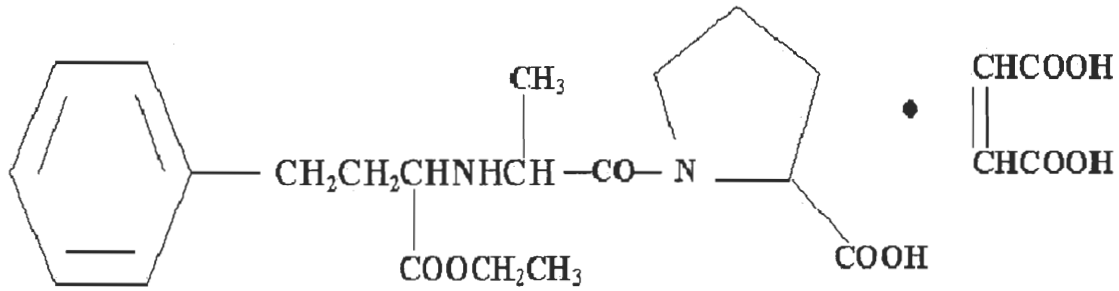

Figure 3. The structural formula of (S)-1-[N-[1-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline•(Z)-2-butenedioate salt, Vasotec® (Enalapril maleate) manufactured and distributed by Merck & Co., Inc., of West Point, PA.

Heart failure is the leading cause of death in older Americans. Merck & Co., Inc. of West Point, Pennsylvania, designed Vasotec® (Enalapril maleate) tablets as a treatment for assuaging the three leading contributors to the failure of the cardiovascular system: hypertension, symptomatic heart failure, and asymptomatic left ventricular dysfunctia. In humans, Vasotec is an angiotensin converting enzyme (ACE) inhibitor. When Vasotec enters the body, it hydrolyzes becoming its active form of enalaprilat that prevents the conversion of angiotensin into the vaso-constricting angiotensin II and, in turn, decreases the production of aldosterone (Merck & Co., Inc., 1997). Currently, Vasotec is the only ACE inhibiting treatment on the market for all three of these cardiovascular dysfunctions.

Following the discovery of the unique cardiovascular effects of this drug, Merck & Co., Inc. pursued preclinical animal studies to evaluate the metabolic, physiologic, and biologic effects and safety of Enalapril maleate. These studies included initial dose-response experiments in mice and rats, which resulted in the establishment of lethality at ≥1000 mg/kg doses attributed to drastic hypotension (Merck & Co., Inc., 1997). Carcinogenic and fertility studies showed no adverse effects in animal studies even at extraordinarily high dosages; furthermore, dog and rat studies proved that enalaprilat remains blocked by the blood brain barrier without collection in bodily tissue (Merck & Co., Inc., 1997). With promising preclinical findings, the FDA approved the Phase One clinical studies of Vasotec by Merck & Co., Inc.

FDA approval of the IND began the longest set of clinical trials with the highest test subject populations ever in the history of FDA regulatory affairs. Clinical trials of Vasotec ran for 10 year's time with many thousands of patients involved in the populations of the trials. During Phase Two and Three clinical trials, Merck & Co., Inc. sponsored multiple investigation centers in Studies of Left Ventricular Dysfunction (SOLVD) Treatment and Prevention Trials. In the first of these placebo-controlled trials, 2,569 patients suffering from symptomatic heart failure randomly were treated with Vasotec or placebo with a resulting 11% decrease in death rates and 30% decrease in the need for hospitalization (Merck & Co., Inc., 1997; Chodoff *et al.*, 1991). The second trial culminated in an extensive five year study of SOLVD Treatment and Prevention with over 4,000

patients suffering from left ventricle dysfunctia being treated with Vasotec. This previously unheard-of population and duration studies further demonstrated the efficacy of Vasotec in decreasing hypertension, reducing the necessity for hospitalization, and lowering projected future heart failure (Merck & Co., Inc., 1997). With such overwhelming data over ten years in support of the efficacy and safety of Vasotec, the FDA approved the Merck & Co., Inc. NDA #01-9309 on July 31, 1996 for injectable Vasotec and NDA #01-8998 for the tablet form of Vasotec concurrently. Globally, Merck & Co., Inc. is the sole provider of this novel ACE inhibiting cardiovascular treatment drug with billions of dollars in revenue each year.

5.3 The Story of DNase I – Pulmozyme (Dornase alfa) by Genentech, Inc.

Figure 4. DNase I – Pulmozyme (Dornase alfa) manufactured and distributed by Genentech, Inc. of South San Francisco, CA.

Cystic fibrosis (CF) is a heretical respiratory disease that causes the collection of thick mucous within the lower respiratory system, which induces reduced respiratory operation and an increase in the chance of pulmonary infections. CF is a life-long disease that results in the early death of sufferers by suffocation from the muocosal fluid pooled within their lungs or the patient succumbs to respiratory tract infection. The expense of constant conventional treatment of CF and the decrease in the quality of life of the sufferer is taxing upon the patient, family, and health care facilities. Genentech, Inc. of South San Francisco, California, has obtained NDA approval by the FDA for Pulmozyme (Dornase alfa) as a treatment for the mucousal build-up within the lungs of CF sufferers. An aerosol inhalant, Pulmozyme is the product of genetic recombination in CHO cells, similar to the techniques used in the production of EPO, to produce the human enzyme deoxyribonuclease I (DNase I), which is responsible for the selective breakdown of DNA (Hoffmann - LaRoche, 1997). Because much of the viscosity of the accumulated mucous is attributed to excess

free DNA, Pulmozyme fluidizes the mucous allowing the sufferer to easily cough up the sputum. Pulmozyme drastically betters the quality of life of sufferers, increases their life expectancy, and decreases health care costs for short-term treatment.

Prior to IND acceptance of Phase One clinical trials, Genentech conducted *in vitro* and animal evaluations to determine the safety and pharmacological as well as biological effects of the inhalation of Pulmozyme. Preclinical trials explored the overdose responses of rats and monkeys at doses up to 100 times more potent than the normal human dose (Hoffmann - LaRoche, 1997). These results suggested correctly that an overdose of Pulmozyme has no adverse effect upon the body. In carcinogenic and fertility studies, no adverse effects were found. Preclinical drug interaction studies demonstrated the ability of other CF drug therapies to be used in conjunction with Pulmozyme without adverse side effects or efficacy negation.

In 1990, the promising preclinical trials helped to expedite and accelerate the IND approval for Phase One clinical trials and the Phase One trials themselves because the metabolic and physiologic effects of the drug in animals had been quickly shown to correlate with the effects in humans. The short-term dose-response studies in Phase One clinical trials revealed that higher doses of Pulmozyme do not result in a paralleled decrease in the rate of infection, instead a dose-response plateau is attained. The dose-response studies combined with the

resulting equivalent percentages of reported placebo-experimental adverse drug experiences as well as the previous animal studies strongly suggested the safety of Pulmozyme. In the same year as Phase I trials commenced and completed, Phase Two trials began with a investigational population of 181 sufferers of CF (Hoffmann - LaRoche, 1997).

> "Phase One trials, overwhelmingly successful, were rapidly forgotten in the blur of activity that occurred in 1990...The amount of data and paperwork generated in such a short time demanded our constant attention for the formulation of the IND for the next phase of trials" (Dinka, 1998).

Phase Three clinical trials, which began in 1992, consisted of 322 patients that were treated with 2.5 mg of Pulmozyme once daily, 321 patients that were given 2.5 mg of Pulmozyme twice daily, and 325 patients provided with a placebo over a six month investigation period (Hoffmann - LaRoche, 1997). These results proved that Pulmozyme aided in the reduction of respiratory infections and thus the effectiveness of the drug, and in August of 1993, the FDA approved the NDA of Pulmozyme by Genentech with the stipulation of a more diversified test population including young and advanced patients with CF. In December of 1993, the FDA granted Genentech permission to publicly market and distribute Pulmozyme.

6. FDA REMOVAL OF DRUG FAILURES

6.1 The Tragedy of Zomax (Zomepirac) by McNeil Pharmaceuticals, Inc.

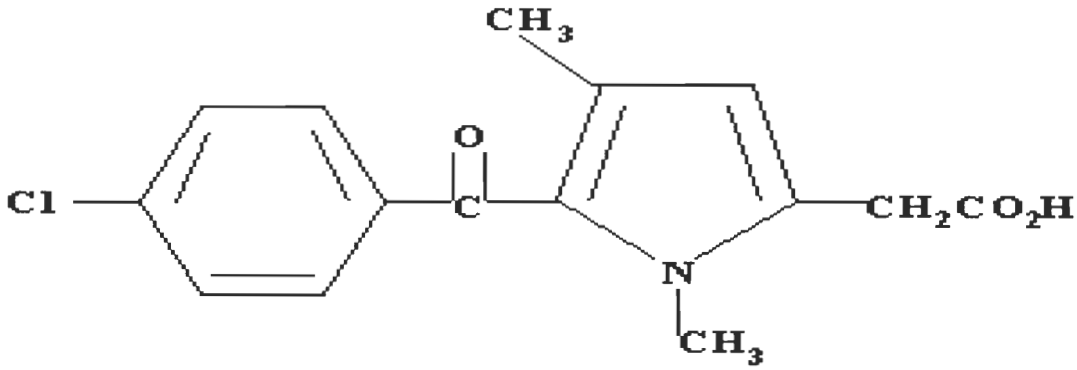

Figure 5. The structural formula of Zomax (Zomepirac sodium) manufactured by McNeil Pharmaceuticals, Inc. of Spring House, PA (US Government, 1983).

McNeil Pharmaceuticals, Inc. of Spring House, Pennsylvania, manufactured 100 mg Zomax (Zomepirac sodium) tablets as an aspirin alternative and applied for approval of IND #10-834 to begin clinical investigations of Zomax in 1974. Investigations of Zomax were aimed at exploring its analgesic properties for the relief of mild to moderate pain in human subjects. Previous preclinical trials attested to the effectiveness of Zomax as a non-steroidal, pain relieving anti-inflammatory; however, the safety of Zomax, specifically surrounding its carcinogenic properties, was not fully elucidated in these trials (US Government, 1983). Animal studies of the carcinogenic properties of Zomax would not be released until after NDA approval. Submitted preclinical trial data supported the FDA approval of the Zomax IND #10-834 in the beginning of 1974.

In July of 1974, Phase one clinical trials began to elucidate the safety and efficacy of Zomax. Clinical trials of Zomax were vast with more than 3, 600

patients being treated with Zomax; however, of those 3,600, only approximately 1000 subjects were given Zomax daily for 1 to 3 months, and only 180 subjects had received treatment daily for over 180 days (US Government, 1983). These double blind studies were well executed and documented but ideally should have contained more placebo-controlled testings. During these clinical trials, few unexpected adverse drug experiences were reported to Investigators. The expected gastrointestinal side-effects of diarrhea and nausea were of no great concern, but one case of mild allergic reaction resulting in an anaphylactic reaction was documented. McNeil Pharmaceuticals explained this case as a result of allergies to aspirin inducing a similar allergic reaction to Zomax. With strong efficacy data and no documented lack of drug safety, McNeil Pharmaceuticals submitted an NDA for the approval of the Zomax (Zomepirac sodium) 100 mg tablets on December 18, 1978.

After brief NDA revision with further study data collected on dose-response of Zomax and its use during pregnancy, the FDA approved NDA #18-236 for the manufacture and distribution of Zomax in the US. Months later, McNeil Pharmaceuticals released data collected from carcinogen studies of Zomax in mice and rats. These results showed adrenal cortex tumor formation in both benign and malignant status attributable to the high doses of Zomax that the test animals were subjected to over time. During the next year, physicians and patient reported numerous cases of anaphylactic reactions to Zomax to both the FDA and McNeil Pharmaceuticals; however, McNeil Pharmaceuticals quickly

attributed aspirin allergies to the Zomax anaphylactic reactions, which physicians should have determined prior to prescribing Zomax. Many of these cases were not being reported in patients with known aspirin allergies. On March 4, 1983, McNeil Pharmaceuticals voluntarily removed Zomax from the market at the behest of the FDA after report confirmation of at least five fatalities and numerous near-fatal anaphylactic reactions because of allergic reactions in patients to Zomax (US Government, 1983). In October of 1983, a subcommittee of the Committee on Government Operations in the House of Representative hearing was convened to evaluate the role of the FDA in this tragedy. The deaths of at least five people could have been prevented had long-term human studies evaluated the allergic effects of Zomax and if McNeil Pharmaceuticals had provided the carcinogenic data prior to NDA approval. This tragic event demonstrates the necessity with which the FDA must remain consistently watchful of all corporations vying for new drug approval.

6.2 The Failings of Serc (Betahistine hydrochloride) by Unimed, Inc.

On November 11, 1966, the FDA approved the New Drug Application #14-241 for Serc (Betahistine hydrochloride) manufactured by Unimed, Inc. Serc received approval as a treatment for the reduction in occurrence of vertigo intervals associated with Meniere's disease. Intense episodic vertigo, sensorineural hearing loss, and limitus characterize Meniere's disease (US Government, 1972). At this time, the physiological cause of Meniere's disease was unknown, and very few treatments for this debilitating, yet non-fatal, disease existed. The action of Serc as an anti-vertigo drug was not well understood. Its clinical action was attributed to its vasodilation effects in the cerebral circulatory system; however, this correlation was not proven as the therapeutic causative agent. Unimed, Inc., submitted the original IND for the investigation of Serc, IND #1244, on September 25, 1963, in double blind clinical trials to assert the safety and effectiveness of Serc in human patients. Double blind trials were suggested because evaluation of Meinere's disease symptoms is highly subjective and individual per patient; therefore, neither patient nor Investigator could know the nature of the drug being administered, placebo or controlled, for an objective symptom prognosis. The clinical trials for Serc were extensive in the numbers of trial populations and collectively suggested efficacy, but a definitive efficacy could not be demonstrated because of the subjective nature of the symptoms and random occurrence of vertigo attacks. The only adverse side-effects that patients reported were nausea, vomiting, and headaches. Based upon this data alone, the

FDA moved to approve the NDA for Serc in 1966 over the objection of the primary care officer.

Over the next three years, doubt mounted concerning the efficacy of Serc, specifically over the results of the main trial upon which approval was based. A House subcommittee hearing was announced upon FDA reappraisal of the NDA data to reevaluate the approval. The FDA reappraisal confirmed the misrepresentation and deficiencies in the data presented in the Serc NDA. The Elia study, which strongly supported the effectiveness of Serc, had broken the double blind curtain and sacrificed the objectivity of the study without reporting the decoding to the Sponsor (US Government, 1972). This clinical blunder was only revealed upon close FDA inspection of the Elia records and personnel.

On November 11, 1970, the FDA published the withdrawal of the Serc NDA approval in the Federal Register to provide the agency with the power to revoke approval of Serc at anytime; however, the FDA allowed Unimed to continue marketing Serc to finance a new round of clinical trials. The FDA was disinterested in the financial status of Unimed but was concerned about removing an effective product from the market and the hands of suffering patients. Because of the unprecedented action of the FDA, a hearing was called before a subcommittee of the Committee on Government Operations in the House of Representatives, which acts as oversight of the FDA, over FDA regulation of the drug Serc on September 25, 1972 (US Government, 1972). The hearing

suggested negligence on the part of Unimed and the FDA, but the subcommittee upheld the FDA ruling with the condition of a stringent time frame for these trials to conclude and future documentation improvements within the administration. The clinical trials continuously demonstrated the safety of Serc, but the efficacy of Serc could not be convincingly proven in a controlled clinical trial. To protect the consumer from further purchasing of an ineffective drug product, the FDA followed through with the 1970 NDA approval withdrawal of Serc and in so doing dictated that NDA approval must be based upon the safety and efficacy of a pharmaceutical product.

6.3 The Disaster of Triazure (Azaribine) by Parke, Davis & Co., Inc.

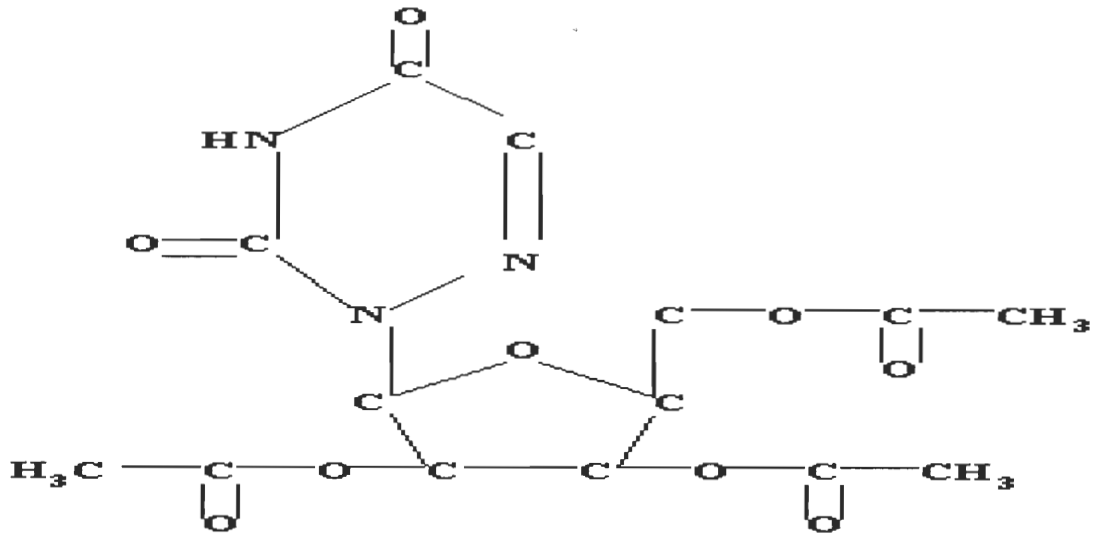

Figure 6. Structural formula of Triazure (Azaribine) manufactured by Parke, Davis & Co., Inc. (Parke, Davis, & Co., 1975)

Originally formulated and filed for approval by Calbiochem, Inc. of San Diego, California, Triazure (Azaribine) received FDA approval for its NDA #16-899 on February 28, 1975, after six years of NDA revisions and resubmissions. Immediately following the announcement of approval, Parke, Davis, & Co., Inc. - a subsidiary of Warner Lambert Co. purchased Triazure from Calbiochem, Inc. The FDA approved the Parke, Davis & Co. supplement to the NDA #16-899 for Triazure production and sale on June 2, 1975 (US Government, 1976). The FDA had approved Triazure (Azaribine) 500 mg tablets as a treatment drug for extremely severe, recalcitrant cases of psoriasis that do not respond to normal topical therapies. Taken orally, Triazure acts as a systemic, anti-mitotic/anti-metabolite drug that acts by interfering with DNA synthesis.

Preclinical and clinical trials supported the effectiveness of Traizure as a treatment for severe cases of psoriasis, but the trials repeatedly fluctuated on the evaluation of the safety of Triazure in both animal and human studies prolonging NDA approval for six years. Preclinical animal studies on the effects of Triazure upon reproduction and fertility indicated that Triazure is toxic to embryos and mutagenic in developing fetuses. In preclinical trials, Triazure was shown to possess some immunosuppression properties and to suppress the central nervous system resulting in fatigue and loss of equilibrium. Aside from these adverse side effects, Calbiochem, Inc. demonstrated that Triazure is highly effective in the treatment of psoriasis. Based upon the dramatic efficacy results, the FDA approved the IND for Triazure. Phase Three clinical trials produced alarming results that had previously not been documented. In a percentage of patients, Triazure induced thromboembolisms (US Government, 1976). Because of this adverse event occurrence in patients prescribed only controlled Triazure and not placebo, Calbiochem, Inc., was unable to gain initial FDA approval of the NDA. The FDA could not evaluate the benefits versus the risks of approving Triazure with the limited data available. Continued trials resulted in similar findings on the safety of Triazure; however, the increased data strongly supported the efficacy of an eight week treatment of severe psoriasis with Triazure resulting in psoriasis remission for up to a year or longer. Calbiochem, Inc. resubmitted the Triazure NDA three times, and the FDA finally approved it based upon the efficacy findings and the condition of a three-year thromboembolism Phase Four study.

Upon NDA approval and subsequent purchase of the drug by Parke, Davis & Co., Parke-Davis avariciously advertised Triazure in medical journals priming the market for Triazure release and themselves for disaster. Within a year's time on August 12, 1976, the FDA ordered Triazure to be removed from the US market and all studies were discontinued because of "its capability to produce fatal blood clots in veins or arteries;" in addition, one patient fatality, one limb amputation, and a number of intravenous and intra-arterial blood clots were reported to the public (US Government, 1976).

> "The importance of the role of the FDA in regulatory affairs for the protection of the consumer became very apparent in the Triazure tragedy...It's a shame that Triazure's distribution couldn't have been prevented prior to such incidents, but I believe that it re-emphasized safety as the primary concern of the industry and administration" (Cinder, 1999).

A hearing was held before a subcommittee of the Committee on Government Operations in the House of Representatives, which as oversight of the FDA questioned the role of the FDA in this disaster of Triazure on October 27, 1976. The subcommittee did not find the FDA negligent in approving the NDA or Phase Four trials but greatly questioned the judgement of the administration. The FDA must exist as the protector of the public against such disasters as the Triazure

story and cannot allow the approval and subsequent marketing of an unsafe product to the public.

7. A GUIDE TO IMPROVING AND MAINTAINING IND & NDA APPROVAL

The following chapter offers guidance to QC/QA personnel, validation firms, and drug as well as pharmaceutical corporations seeking FDA approval for an IND or NDA. This guide is meant to aid in preparing for an IND, planning clinical trial investigations, writing an IND or NDA for submission, and maintaining NDA approval status. The table format of these guidelines offers the user an easy means to proceed through them in a checklist manner to verify that they have been met. These guidelines have been drawn from the experience and knowledge gleaned from the drug case studies previously mentioned, the many FDA and government regulations that have been reviewed, and communication with QC, QA and validation experts.

Table 2. Guidelines for improving and maintaining FDA approval for all IND's and NDA's submitted (ICH Guidelines for Good Clinical Practices (E6), 1998).

A Guide to Improving & Maintaining FDA Approval	
Guidance	**Achieved (Y/N)**
Standard Operating Procedures (SOP's) must be established for all facets of a facility producing the investigational drug.	
All cGMP's must be met by the manufacturer of the investigational drug.	
Document tracking and coding systems should be in-place.	
All equipment, procedures, facilities, and ingredients involved in the manufacture of an investigational drug must be validated to verify FDA standards have been met.	
All ingredients of the final product must be quality certified, traceable via a coding system and documented within the batch record.	
All outside companies involved in the manufacture of the investigational drug must be audited for GMP compliance, FDA standards, and product quality assurance.	
All necessary instruments involved within the production, analysis, and packaging of the drug product must be annually calibrated.	
All facilities, equipment, and procedures must have and meet established, scientifically proven acceptance criteria.	

A Guide to Improving & Maintaining FDA Approval (continued)	
Guidance	**Achieved (Y/N)**
The effects of the investigational drug carcinogenically, mutagenically, and reproductively must be determined in preclinical trials prior to Phase One IND submission.	
Preclinical trials should begin in *in vitro* studies as well as rats and/or mice and progress to larger animals more closely related to humans such as dogs or monkeys to better establish the safety limits and efficacy of the drug prior to pursuit of an IND, a costly and time consuming endeavor.	
All preclinical trial data should be presented to the FDA in the initial IND for an objective evaluation of the safety and efficacy status of the product.	
The responsible parties should sign all sections of an IND including the IB, protocols, and CRF's.	
The IB should document all current scientific knowledge concerning the product under investigation.	
Test subjects should receive informed consent forms to sign, statements of accident insurance, and product information as documented in the IB.	
An agreement should exist outlining the handling of expenses incurred during trials between the Sponsor and Investigator.	
The IRB or IEC must approve all relevant sections of the IND such as the consent forms, accidental insurance, protocols, CRF, etc. This approval must be documented in the IND.	
Sponsor contacts must be clearly stated with all information for the reporting of results, problems, or questions stated in the IB.	
Methods of analysis for the determination of physiological, pharmacological, and biological effects of the product in humans must be stated in the IB, IND and final NDA.	
Acceptable limits must be set and documented in the IND for the results of the laboratory and clinical assays.	
Certification of validation, quality control and training must be ensured and documented for all facilities conducting analysis of samples.	
Meeting FDA labeling regulations, sample product labels must be included within an IND.	
The packaging and labeling of the product for market release must be strictly controlled and include quantity, ingredients, dosage, directions, warnings, and expiration dates. All packaging must be tamper resistant.	
The specific product lot #'s to be used in trials as well as product quality approval should be documented in an IND. Product potency and identity should also be noted for each of the lot #'s involved with the trials.	
Detailed protocols must document the procedures for handling, administering, dosages and storing of investigational drug (all of which will eventually be included within the physician's and package informational insert).	
All trials should be blind studies and random. Sponsors and analysts do not know if patient received product or placebo. A protocol for the method of randomizing the patient population and breaking the blind code in an emergency must be established.	

A Guide to Improving & Maintaining FDA Approval (continued)	
Guidance	**Achieved (Y/N)**
The method of statistical analysis of all data and the corporation conducting the analysis must be specified in an IND.	
Agreements with the investigational institution and Investigator should be included in the IND.	
A confidential log of all possible pretrial candidates must be kept for the evaluation of random and objective subject selection.	
Confidential documentation of subject enrollment should be maintained by the Investigator noting the date, patient identification code, and prescribed drug identification code.	
A confidential identification log for all test patients must be kept referencing the drug code that they have been administered. This drug identification code is the means of identifying the status of the drug (placebo or actual) in this blind study.	
Investigators are responsible for tracking all amounts of investigational drug provided to them by Sponsor and for documenting the amounts of drug prescribed to, used by, and returned by each patient.	
All patient contact including telephone conversations, letters and documented visit reports should be provided to the Sponsor for review of protocol deviations and adverse drug experiences.	
Biological samples (ie urine, blood, feces, spinal fluid, biopsies, etc.), methods of analysis of these samples, certification of the laboratories conducting the analysis, and results of laboratory tests must be documented by the Investigator and submitted to the Sponsor. If possible, samples should be maintained for any future analysis desired and repeating of the conducted test if so desired by the Sponsor.	
Investigators must document all actions taken, all deviations with explanations conducted during the trial, and the results accumulated for submittal to the Sponsor.	
Completed CRF's must be signed and dated and include all collected trial data, original documents generated during the trial, an extensive patient history, and any deviations that occurred during the study.	
Timely status reports must be submitted to the IRB/IEC at specified intervals (normally annually).	
Annual reports must be made to the FDA within 60 days of the anniversary of the day the IND went into effect	
Changes or amendments to the IND, especially to the IB and protocols, must be reported as soon as possible to the Investigator, IRB/IEC, and FDA. All parties involved must approve these changes and amendments.	
All trial reports and the responses to these reports from the IRB/IEC must be documented for future submittals of IND's.	
The Investigators are responsible for immediately reporting any problems, adverse drug experiences or unexpected drug side effects to the Sponsor in a formal document. The Sponsor is responsible for reporting these findings to both the IRB/IEC and FDA.	
The standardization of statistical analysis of data not only throughout the trials but also throughout the industry would ensure objective, unadulterated statistical data.	

A Guide to Improving & Maintaining FDA Approval (continued)	
Guidance	**Achieved (Y/N)**
All unused investigational drugs provided to Investigators must be destroyed. Destruction must be documented and provided to the Sponsor.	
A final trial close-out report should be filed documenting the completion of trial activities, culminating all collected data, and signed by the Investigator as well as Sponsor.	
Final trial reports must be provided to the IRB/IEC from both the Investigators and Sponsors summarizing trial activity, results, and completion.	
A clinical trial study report must be written to document the analysis of all collected and the conclusions drawn from the analysis.	
Conclusive safety should be demonstrated prior to Phase Two clinical trials and ideally shown following preclinical trials.	
Conclusive evidence of drug effectiveness must be demonstrated by the end of Phase Three clinical trials and prior to NDA submission. NDA approval should not be risked if either safety or effectiveness is in question. Phase Four clinical trials should not be considered during NDA submission and review because of the legal issues involved.	
The drug substance of the investigated drug must be stated with a detailed drug production, testing, and packaging methodology as the manufacturing scheme for the drug in the NDA. The drug products or ingredients of the pharmaceutical are also specified in the drug substance section.	
The pharmacological, biological and toxicological effects of the drug determined in the *in vitro*, animal, and human studies must be documented in a NDA.	
Collected throughout the entire clinical trial investigations, all clinical data and the analysis of this data must be submitted within the NDA.	
The NDA details the final stability runs on manufactured drug and analytical methods for data evaluation.	
The Sponsor must submit three signed copies of this voluminous document to the FDA: an Archival copy, Review copy, and Field copy.	
During the distribution and sale of the drug product, incidents may be reported to the prescribing physicians and manufacturers of adverse drug experiences. Any serious, unexpected, or statistically continuous reaction must be reported to the FDA immediately.	
Lot testing of final product must be routinely conducted to ensure and document the sterility, activity, quality, and safety of the pharmaceutical. This routine testing also verifies the process and product stability through comparison to in-place standards of reference that have been proven as scientifically sound.	
Manufacturers must submit NDA – Field Alert Reports if a lot or batch is found to be improperly labeled or adulterated by contamination, heat, etc.	

A Guide to Improving & Maintaining FDA Approval (continued)	
Guidance	**Achieved (Y/N)**
Annual reports must be submitted to the FDA including a product summary similar to the NDA summary, marketing as well as shipping data, changes in the manufacturing scheme under change control SOP's, clinical and non-clinical data, variations in drug compositions under change control SOP's, and status reports on any conducted post-marketing investigations.	
All advertising and promotional materials must be submitted to the FDA for approval.	
IND and NDA composition and revision produce volumes of paper. A method of digital transfer, transmission, and submission of these voluminous documents would expedite approval.	
Compliance with all FDA CFR, ICH guidelines and OSHA safety regulations ensures smooth and timely FDA approval if the safety and effectiveness data for the investigational drug is convincing. Maintaining these standards is the best way to ensure consistent FDA approval and retention of that approval as well as the safety and health of the public.	

8. THE SOCIETAL IMPACTS & ECONOMIC RAMIFICATIONS OF FDA REGULATORY ACTIONS

FDA regulatory actions have become commonplace within society today to the point where one does not question whether or not the drugs that one is taking for a headache or common cold are safe and effective; however, the societal impact of the FDA has drastic ramifications upon the individual, the economy, drug and health care industries. To ensure public safety, the FDA has developed a defined approval process commencing with preclinical trials, advancing to IND approval as well as clinical investigations, and ending with NDA approval. Detrimental to the consumer, this regulatory approval process is a long-term time and cost investment by manufacturers, clinical investigators/institutions, and the FDA. The time committed to qualifying and re-qualifying investigations into the safety and efficacy of high demand drugs is time that could be spent administering those drugs to patients whose lives may be saved by receipt of such therapy. The devastation of the Acquired Immune Deficiency Syndrome (AIDS) epidemic has brought this problem to the forefront, and the FDA rapidly approved the IND's and NDA of the drug AZT for the treatment of AIDS. This accelerated approval rate did not diminish the standards of safety and efficacy. Unfortunately, this acceleration has been unable to continue for example with the approval of Vasotec. Clinical trials lasted ten years with heart failure remaining as the number one cause of death in older Americans. In order for the FDA to function in the best interests of the patient, a balance must be struck between approval time and patient health.

The expenses that are incurred during trials and the approval process limit the companies that apply for approval. Potentially novel treatments in companies with a low financial infrastructure are suppressed by the adamantine costs required to pursue approval. For example, Amgen, Inc., was close at times to terminating clinical trials of Epogen because of a lack in funds; fortunately, for patient suffering from kidney failure, Amgen, Inc., did no halt trials. The Orphan Drug Plan was a step in the appropriate direction for the FDA. However, this plan only addresses tax breaks for companies pursuing drug investigations and approval for the treatment of rare diseases and disorders, which have a market that will not recuperate the money invested in the manufacture and approval of the drug. The cost to the manufacturer is normally in the tens, if not hundreds, of millions of dollars to reach the stage of possessing approval to market a drug product. Many companies are based solely upon the pursuit of approval for one product; if the approval process stalls or falters completely, companies may be shutdown due to bankruptcy and lack of an approved marketable product. Companies that obtain FDA approval of an NDA recuperate lost expenses through an increase cost to the consumer for the product and an increased health care cost. Are the time and expense to ensure safety and effectiveness too great for the consumer?

The time and expenses dedicated to safety and efficacy verification are necessary to ensure consumer protection, and the highest responsibility resting upon the government, specifically the FDA, is to protect the public from the unknown and invisible threats that adulterated, unsafe, and ineffective drugs possess. The safety of pharmaceuticals is of the utmost importance to which the Zomax, Triazure, Thalidomide,

and Sulfinamide tragedies attest. Careful examination could have prevented the loss of lives resulting from these unfortunate drug disasters.

In general, when the FDA approves a drug product, the health care expenses decrease. The result of the introduction of Vasotec to the market was to reduce the number of patient hospitalizations and decrease in the risk of mortality in patients suffering from heart failure, hypertension, and left ventricle dysfunctia. The introduction of Pulmozyme decreased the amount of required therapy for CF patients and dramatically increased their quality of life. Epogen also increased the daily quality of life in renal failure patients while reducing the need for prolonged hospitalization and dialysis. Amgen, Inc., conducted post-approval studies during the early 1990's to evaluate the effect Epogen has had on the mortality rate of renal failure patients. The dramatic statistical data demonstrates that the risk of mortality has decreased once Epogen had been administered (*Figure 7*). The overall societal benefits are plentiful from a decrease in hospitalization to a reduced health care cost to a greatly improved quality of life.

The influence of FDA assurance that a drug product is safe and effective demonstrated by NDA approval stimulates consumer confidence in product and prosperity for industries economically. FDA approval bolsters the confidence of the public as well as physicians in a drug product, and when coupled with a ripe market, consumer and physician confidence increase the use and thus demand for a product. In 1998 alone, Epogen sales equaled $1.382 billion, a 19% increase from 1997 (Amgen, Inc., 1998). The global sale of Vasotec in 1996 was more than $2 billion (Merck & Co.,

Inc., 1996). Economic prosperity and high sales of a drug product correlate with an increase in job opportunities within the US, for example, Amgen, Inc., broke ground in 1996 in Longmont, CO, on a new manufacturing facility for Epogen, thus economic prosperity is spread from the industry to the public. Increased economic prosperity, in turn, increases the overall societal quality of life through the economy. The societal benefits and economic prosperity fostered by safe and effective drugs far outweigh the initial costs, time, and regulatory affairs.

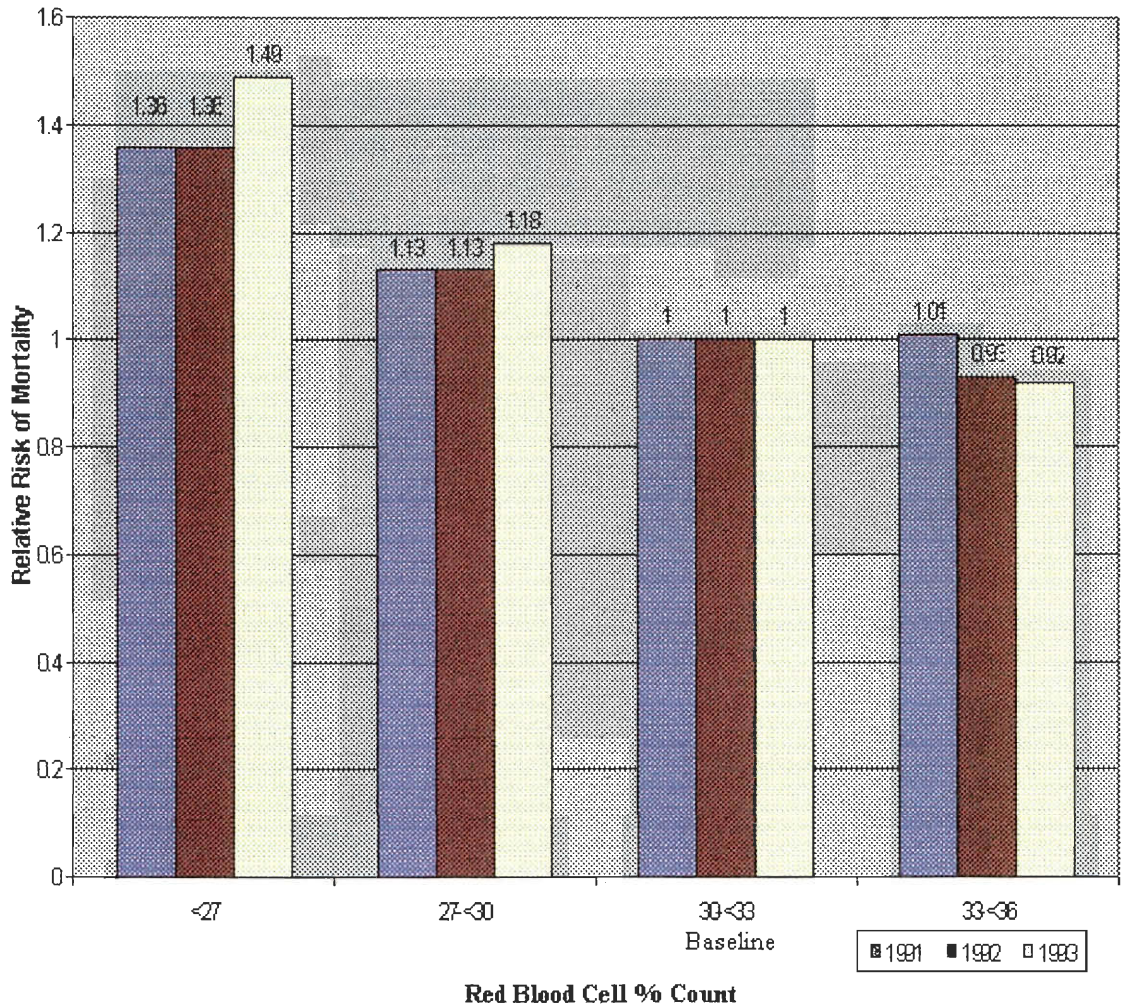

Figure 7. The result of a three-year study of the effects of Epogen on the risk of mortality to renal failure patients was published by Amgen in the Amgen 1998 Annual Report (Amgen, Inc., 1998).

9. CONCLUSIONS

The initiation of the founding of the Food and Drug Administration was a result of the great tragedies and health risks of the early twentieth century; a necessity for consumer protection from adulterated, unsafe, impure, and ineffective drug products pervaded the United States and demanded government intervention. As such, the government established the FDA as a reactionary police force of the food and drug industries to ensure public health and safety. After several decades of establishing itself, the FDA became less of a reactionary measure and more of a preventative measure throughout these industries. Through published regulations such as the cGMP's, GCP's, and the rest of 21 CFR, the FDA has unified standards of acceptability across the United States and continues to work with the ICH to produce a globally universal set of standards for all drug products. The years of trial and error in the FDA approach towards clinical trials and the approval process has ended with the establishment of minimum standard requirements to be met by all drugs. Through the constant and vigilant examination of both new and approved drug products, the FDA has shouldered the burden of responsibility for the protection of the consumer, yet the true responsibility for the safety and efficacy of all investigational drugs, as well as the potency and purity of the product remains within the hands of the manufacturer and sponsor vying for drug approval and approval maintenance. Future improvements must delegate this responsibility between the FDA and drug industry to avert any future drug disasters.

This Interactive Qualifying Project (IQP) has set forth guidelines and advice as to how companies can better their success rates for drug product approval during and

following clinical trials with the aim of attaining and maintaining that approval. The suggestions offered in this IQP will hopefully be of use to companies in such pursuits. Advice addressed to validation considerations during the approval process and beyond with its attention to current GMP's and software/control system validation should also be used in these pursuits. The tragic case studies of Triazure and Zomax presented here demonstrate the continued need for a watchful guardian of the people, protecting the public from the invisible menaces of untested and unsafe drug products. With the hopes of improved small business funding and increased approval times, the societal and economic impact investigation of the entire FDA regulatory affair has demonstrated the societal and economic benefits to all people from FDA approval.

Scarcely a moment passes by that someone in the US is not being administered some form of drug product. People have come to rely upon and trust fully the medication that they buy in their local pharmacy or that their physicians prescribe to them to relieve pain, disease or infection as being safe and effective. This bond is broken whenever a drug is released that has not met every FDA standard to the utmost assurance that this drug will be effective and will not place the public at risk. The FDA maintains this bond even as the science of biotechnology, pharmacology, and drug production has expanded exponentially over the last century and continues in an ever-dizzying pace forward. A need for the effective regulation of drug approval and distribution continues with the concern of the safety, health, and trust of the American people; more so today than ever before, the FDA stands ready to face the regulatory and statutory difficulties of the regulatory affairs of the United States and the world.

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11.1 Appendix I – Draft Sample of an Installation Qualification (IQ)

INSTALLATION QUALIFICATION

FOR THE

PURIFIED WATER SYSTEM

AT

XXX
XXX, XXX

Total Number of Pages: 40
(Including Cover & TOC)

SAMPLE DRAFT

Prepared by / Date

_____
XXX

Revision: XXX

Date: XXX

Approval

Approved By:

Engineering _____ Date _____

Validation _____ Date _____

Quality Assurance _____ Date _____

TABLE OF CONTENTS

1 PURPOSE

The purpose of this Installation Qualification (IQ) Protocol is to provide XXX., documented verification that the reverse osmosis/deionized water system's hardware and software have been installed per manufacturer/ XXX design specifications.

2 SCOPE

This qualification activity applies to the Installation Qualification of the reverse osmosis/deionized water system located at XXX.

2.1 The Reverse Osmosis system is identified by the following:

Manufacturer: XXX

2.2 The CDI system is identified by the following:

Manufacturer: XXX

2.3 The Reverse Osmosis/Deionized water system is installed in the following location:

XXX in XXX, XXX

3 REFERENCES

XXX

6 SYSTEM DESCRIPTION

XXX

SAMPLE DRAFT

7 DOCUMENTATION VERIFICATIONS

7.1 Equipment Documentation

The following is a list of documentation available for the RO/DI Water System. This list includes (as appropriate) installation drawings, manuals, specifications, and electrical schematics, controller connections, or P&ID drawings. All documents will be reviewed to ensure that they are complete, correct and current.

Document Change Control: **Reviewed By/Date**

Title: _____ _____

Change Control No.: _____ Effective Date: _____

Location: _____

Drawing Number/Title/Date/Revision/Location:

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

7 DOCUMENTATION VERIFICATIONS (continued)

7.1 Equipment Documentation (continued)

Manuals/Title/Date/Revision/Location: **Reviewed By/Date**

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Specifications:

Reviewed By/Date

_____ _____

_____ _____

_____ _____

_____ _____

_____ _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____ _____

7 DOCUMENTATION VERIFICATION (continued)

7.2 SOP's

Calibration: **Reviewed By/Date**

Title: _____ _____

SOP No.: _____ Effective Date: _____

Location: _____

Preventative Maintenance:

Title: _____ _____

SOP No.: _____ Effective Date: _____

Location: _____

Operation:

Title: _____ _____

SOP No.: _____ Effective Date: _____

Location: _____

Change Control:

Title: _____ _____

SOP No.: _____ Effective Date: _____

Location: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

7 DOCUMENTATION VERIFICATION (continued)

7.2 SOPs (continued)

Sanitization: **Reviewed By/Date**

Title: _____ _____

SOP No.: _____ Effective Date: _____

Location: _____

Water Sampling:

Title: _____ _____

SOP No.: _____ Effective Date: _____

Location: _____

Filter Integrity Verification:

Title: _____ _____

SOP No.: _____ Effective Date: _____

Location: _____

Discrepancy Resolution/Corrective Action Plan:

Title: _____ _____

SOP No.: _____ Effective Date: _____

Location: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

7 DOCUMENTATION VERIFICATION (continued)

7.2 SOPs (continued)

Environmental Monitoring: **Reviewed By/Date**

Title: _____ _____

SOP No.: _____ Effective Date: _____

Location: _____

Comments/Observations/Conclusions:

SAMPLE DRAFT

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS

8.1 System P&ID Verification

Objective:

The objective of this verification is to ensure that all system components have been properly connected, tagged, identified, and are in accordance with manufacturer's specifications and/or engineering drawings.

Procedure:

Using the system P&ID, perform a visual check of all system components. Confirm that all components are clearly identified and in agreement with the specifications and/or engineering drawings. Document all drawings and references.

References Required:

XXX

Acceptance Criteria:

Each system component must be properly tagged or identified, and installed as per the specifications and/or engineering drawings.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.1 System P&ID Verification (continued)

Installation Verifications

System P&ID	Installation as Specified (Yes/No/Comments)	Verified By/Date
XXX		
XXX		

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.2 Utilities Verification

Objective:

The objective of this verification is to ensure that for each utility required for the system, all the as-found conditions comply with the specifications. Information about the utilities not specified by the manufacturer or by XXX will be recorded as baseline information.

Procedure:

For each utility listed record the as-found condition in the specification verifications data sheet. Record the procedure used with the codes listed in this protocol.

References Required:

XXX

Acceptance Criteria:

For each utility required for the system, all the as-found conditions shall comply with the specifications, as noted.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.2 Utilities Verification - Electrical Requirements (continued)

Description: Electrical Requirements

Specification Verifications

Item	Specification	As-Found	Verification Procedure	Verified By/Date
Electrical Requirements for the RO System				
Voltage/Phase/Frequency	XXX			
Electrical Requirements for the RO System Control Panel				
Voltage/Phase/Frequency	XXX			
Electrical Requirements for the Booster Pump				
Voltage/Phase/Frequency	XXX			
Electrical Requirements for the UV Disinfection Unit				
Voltage/Phase/Frequency	XXX			
Electrical Requirements for the CDI System				
Voltage/Phase/Frequency	XXX			
Electrical Requirements for the Distribution Pump				
Voltage/Phase/Frequency	XXX			
Electrical Requirements for the UV Disinfection Unit				
Voltage/Phase/Frequency	XXX			
Electrical Requirements for the Distribution Pump				
Voltage/Phase/Frequency	XXX			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.2 Utilities Verification - Electrical Requirements (continued)

Description: Electrical Requirements

Specification Verifications

Item	Specification	As-Found	Verification Procedure	Verified By/Date
Electrical Requirements for the UV Disinfection Unit				
Voltage/Phase/Frequency	XXX			
Electrical Requirements for the UV Disinfection Unit				
Voltage/Phase/Frequency	XXX			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.2 Utilities Verification - Feed Water Requirements (continued)

Description: Softened Feed Water Requirements

Specification Verifications

Item	Specification	As-Found	Verification Procedure	Verified By/Date
Feed Water Requirements	XXX			
Feed Water Maximum	XXX			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.3 System Components

Objective:

The objective of this verification is to ensure that for each component required for the system, all of the as-found conditions comply with the specifications and that the components required for this system are installed as specified by the manufacturer and/or XXX. Information about the components not specified by the manufacturer or XXX will be recorded as baseline information.

Procedure:

For each component listed, record the as-found condition in the specification verification data sheet(s). Record the procedure used with the codes listed in this protocol.

Verify proper component installations by comparing the components as installed to the approved or as-built drawings and/or system specifications. For each component, record in the installation verification data sheet(s) the items checked and references used.

References Required:

XXX

Acceptance Criteria:

For each component required for the system, all of the as-found conditions shall comply with the specification, as noted. For each component required for the system, the installations and connections are as specified in the system specifications and/or the appropriate drawings.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.3 System Components - Tank

Description: Purified Water Storage Tank w/ Spray Balls

Specification Verifications

Item	Specification	As-Found	Verification Procedure	Verified By/Date
Manufacturer	XXX			
Model Number	XXX			
Tag Number	XXX			
Material of Construction	XXX			
Range	XXX			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.3 System Components – Reverse Osmosis Unit

Description: Reverse Osmosis Unit

Specification Verifications

Item	Specification	As-Found	Verification Procedure	Verified By/Date
Manufacturer	XXX			
Model Number	XXX			
Tag Number	XXX			
Material of Construction	XXX			
Array	XXX			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.3 System Components – Continuous Deionizer Unit

Description: Continuous Deionizer Unit

Specification Verifications

Item	Specification	As-Found	Verification Procedure	Verified By/Date
Manufacturer	XXX			
Model Number	XXX			
Tag Number	XXX			
Material of Construction	XXX			
Setup	XXX			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.3 System Components – UV Sterilizer

Description: Ultraviolet Sterilizer

Specification Verifications

Item	Specification	As-Found	Verification Procedure	Verified By/Date
Manufacturer	XXX			
Model Number	XXX			
Tag Number	XXX			
Material of Construction	XXX			
Wavelength	XXX			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.3 System Components – Valves

Specification Verifications

Tag Number	Manufacturer	Model #	Size	Installed As Specified? (Y/N)	Verification Procedure	Verified By/Date
XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

8 SPECIFICATION AND INSTALLATION VERIFICATIONS (continued)

8.3 System Components – Instruments

Specification Verifications

Tag No.	Description	Manufacturer	Model No.	Range	Installed as Specified? (Yes/No)	Verified By/Date
XXX	XXX	XXX	XXX	XXX		
XXX	XXX	XXX	XXX	XXX		
XXX	XXX	XXX	XXX	XXX		
XXX	XXX	XXX	XXX	XXX		
XXX	XXX	XXX	XXX	XXX		
XXX	XXX	XXX	XXX	XXX		
XXX	XXX	XXX	XXX	XXX		

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

9 HYDROSTATIC TESTING VERIFICATION

Objective:

The objective of this verification is to ensure that Hydrostatic Testing has been performed successfully as required and all of the related documents are available.

Procedure:

Obtain the relevant hydrostatic testing records. Attach a copy of the procedure and all of the test results to this protocol.

References Required:

None.

Acceptance Criteria:

Hydrostatic Testing has been successfully performed and documented as required.

Acceptance Criteria Met: Yes ____ No ____ **Initials/Date: _____**

Results:

Hydrostatic Testing Requirements	Applicable Components	Test Results (Attach Pertinent Documentation)	Verified By/Date
All Pressure Vessels			
USP Water Welded Tubing			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

10 PASSIVATION VERIFICATION

Objective:

The objective of this verification is to ensure that Passivation of the RO/DI System has been performed successfully as required and all of the related documents are available.

Procedure:

Obtain the relevant Passivation Testing records. Attach a copy of the procedure and all of the test results to this protocol.

References Required:

None.

Acceptance Criteria:

Passivation Testing has been successfully performed and documented as required.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

11 SLOPING VERIFICATION

Objective:

The objective of this verification is to ensure that all distribution lines are properly sloped and that there are no dead legs present. (Note: Dead legs present in the distribution lines result in stagnant water and hence possible bacterial contamination.)

Procedure:

With the aid of a level bar, verify that all distribution lines are properly sloped.

References Required:

None.

Acceptance Criteria:

All distribution lines are properly sloped, and there are no evident dead legs.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

12 SPECIFICATION AND INSTALLATION VERIFICATIONS (COMPUTER-RELATED SYSTEMS)

12.1 System Components

Objective:

The objective of this verification is to ensure that for each component required for the system, all of the as-found conditions comply with the specifications. Information about the major components not specified by the manufacturer or XXX will be recorded as baseline information.

Procedure:

For each component listed, record the as-found condition in the specification verification data sheet(s). Record the procedure used with the codes listed in this protocol.

References Required:

XXX

Acceptance Criteria:

For each component required for the system, all the as-found conditions shall comply with the specifications, as noted.

Acceptance Criteria Met: Yes ____ No ____ **Initials/Date: _____**

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

12 SPECIFICATION AND INSTALLATION VERIFICATIONS (COMPUTER-RELATED SYSTEMS) (continued)

12.1 System Components (continued)

Specification Verifications

Component	Manufacturer	Model Number	Serial Number	Verified By/Date
XXX	XXX	XXX		

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

12 SPECIFICATION AND INSTALLATION VERIFICATIONS (COMPUTER-RELATED SYSTEMS) (continued)

12.2 Wiring and Cabling Verification

Objective:

The objective of this verification is to ensure that all wiring and cabling to the system has been properly connected, tagged, identified, and is in accordance with manufacturer's specifications and/or engineering drawings.

Procedure:

Using the wiring and cabling diagrams, perform a visual check of all wiring connections to the system. Confirm that all wire connections are clearly identified and in agreement with the specifications and/or engineering drawings. Document all drawings and references.

References Required:

XXX

Acceptance Criteria:

Each wiring connection must be properly tagged or identified, and wired as per the specifications and/or engineering drawings.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

12 SPECIFICATION AND INSTALLATION VERIFICATIONS (COMPUTER-RELATED SYSTEMS) (continued)

12.2 Wiring and Cabling Verification (continued)

Installation Verifications

Electrical Schematics	Installation as Specified (Yes/No/Comments)	Verified By/Date
XXX		
XXX		
XXX		
XXX		
XXX		

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

12 SPECIFICATION AND INSTALLATION VERIFICATIONS (COMPUTER-RELATED SYSTEMS) (continued)

12.3 Input / Output Verification

Objective:

The objective of this verification is to ensure that all Input / Output points are addressed properly and are connected to the field devices as per manufacturer specifications.

Procedure:

Exercise all I/O points specified in the attached I/O lists using the prioritized list of procedures below. Record the procedures used for each I/O on the attached lists. Verify that points specified as spare are not being utilized.

Input Test Procedures:

- I.1 Manipulate pushbutton or switch from the control panel(s).
- I.2 Simulate input by isolating field device and forcing a response.
- I.3 Simulate input by manipulation of process variables.
- I.4 Simulate the input with the Software Utility.
- I.5 Input verified during calibration of field device.
- I.6 Confirmed during the FAT or SAT testing.

Output Test Procedures:

- O.1 Simulate output with the Software Utility.
- O.2 Simulate output by manipulating process variables and/or changing set points.
- O.3 Simulate output by forcing associated input.
- O.4 Confirmed during the FAT or SAT testing.

References Required:

XXX

Acceptance Criteria:

All input and output points are addressed properly and I/O points designated as spare are not being utilized as outlined on the following pages.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

12 SPECIFICATION AND INSTALLATION VERIFICATIONS (COMPUTER-RELATED SYSTEMS) (continued)

12.3 Input / Output Verification (continued)

RO Control System Input Module:

Address	Description	PIN	Actual Results Observed	Procedure	Verified By/Date
XXX	XXX	XXX			
XXX	XXX	XXX			
XXX	XXX	XXX			
XXX	XXX	XXX			
XXX	XXX	XXX			
XXX	XXX	XXX			
XXX	XXX	XXX			
XXX	XXX	XXX			

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

13 SOFTWARE

13.1 Software Backup, Archiving, and Version Verification

Objective:

The objective of this verification is to determine that the installed ladder logic program version number, archiving, and availability of the backup copy of the installed version.

Procedure:

Contact responsible personnel to determine the archiving procedure. Determine the version from the existing installed version and verify a backup copy of that program. If no version number exists, assign a version number to the validated program.

References Required:

None.

Acceptance Criteria:

The RO/DI Water System ladder logic program is labeled with its name and version number. A backup copy of the program is stored on a floppy disk and in hard copy form in a designated storage location with responsible personnel identified. The version installed on the system matches the soft and hard backup copies.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

13 SOFTWARE (continued)

13.1 Software Backup, Archiving, and Version Verification (continued)

Actual Results:		**Verified By/Date**
Responsible Personnel:	_____	_____
Program Backup Media:	_____	_____
Program Backup Location:	_____	_____
Assigned Version Number of Installed and Backup Software:	_____	_____
Installed Version is Identical to the backup Soft Copy on File:	Yes: _____ No: _____	_____
Installed Version is Identical to the Backup Hard Copy on File:	Yes: _____ No: _____	_____

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

13 SOFTWARE (continued)

13.2 Structural Verification of Software

Objective:

The objective of this verification is to examine the application code for completeness, clarity, and consistency of annotation, program modularity, consistency of structure, and identification of dead (non-executable) or redundant code.

Procedure:

Review and document the installed version of the RO/DI Water System ladder logic program including the title and version number. Examine the program's annotation, program modularity, and consistency of the structure. Identify all dead code.

References Required:

Vendor Evaluation Form.

Acceptance Criteria:

The application source code has consistent structure. Subroutines are used when appropriate to isolate repetitive events. The program utilizes modular structure, and the modules are defined. Each rung is annotated. Annotation is complete and consistent throughout the program. There is no dead code or redundant code.

Acceptance Criteria Met: Yes ____ No ____ **Initials/Date: _____**

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

13 SOFTWARE (continued)

13.2 Structural Verification of Software (continued)

Actual Results:

Item	Specification	Evaluation As-Found	Verified By/Date
Annotation	Complete, clear, and consistent thought		
Modularity and Structure	Modularity is utilized appropriately. Structure is consistent throughout.		
Dead Code	No apparent dead code.		

Comments/Observations/Conclusions:

Completed By: _____ **Date:** _____

SAMPLE DRAFT

14 APPENDICES

14.1 Appendix I - Signature Identification Log Sheet

This log sheet is a record of each individual who signs or initials any page included in the Installation Qualification documents. Each person shall be identified by typed or printed name, full signature, and written initials, department represented (Quality Assurance, Engineering, Validation, Contractor, etc.).

NAME (type or print)	INITIALS	SIGNATURE	DEPARTMENT

14.2 Appendix II - Test Instrumentation Calibration Certificates

Test Equipment Description	Manufacturer	Model No.	Serial No.	Protocol Test No.	Instrumentation Use	Calibration No.	Calibration Date	Calibration Due Date	Verified By/Date

14.3 Appendix III - Attachments

14.3 Appendix III - Attachments

11.2 Appendix II – Draft Sample of an Operational Qualification (OQ)

OPERATIONAL QUALIFICATION

FOR THE

PURIFIED WATER SYSTEM

AT

XXX
XXX, XXX

Total Number of Pages: 22
(Including Cover & TOC)

Prepared By / Date:

_____

XXX

Revision: XXX

Date: XXX

Approval

Approved By:

Engineering/Maintenance _____ Date _____

Manufacturing _____ Date _____

Quality Assurance _____ Date _____

TABLE OF CONTENTS

1 PURPOSE

The purpose of this Operational Qualification (OQ) Protocol is to provide XXX, documented verification that the reverse osmosis/deionized water system's hardware and software operate per manufacturer/XXX design specifications.

2 SCOPE

This qualification activity applies to the Operational Qualification of the reverse osmosis/deionized water system located at XXX.

2.1 The Reverse Osmosis system is identified by the following:

Manufacturer: XXX

2.2 The CDI system is identified by the following:

Manufacturer: XXX

2.3 The Reverse Osmosis/Deionized water system is installed in the following location:

XXX in XXX, XXX

3 REFERENCES

XXX

4 RESPONSIBILITIES

4.1 XXX has the overall supervisory responsibility for the Validation Activities.

4.2 XXX has the responsibility for providing the operators, specialists where required (i.e. licensed electrician), materials, and consumables required for the operation of the system.

4.3 XXX has the responsibility for the execution of this protocol, collecting the test data, signing off the test data sheets and analysis of the test results.

4.4 XXX has the responsibility of preparing and approving a summary report describing the results of the installation/operation qualification exercises.

4.5 XXX has the responsibility of preparing this Operational Qualification protocol.

5 CODES AND ABBREVIATIONS

In the Operational Qualification (OQ), the following abbreviations are used to describe procedure and information code:

Procedure:	VIS	=	Visual Examination
	SPEC	=	Specification from vendor (Spec. Sheet, written Cert., etc.)
	AUDIT	=	Audit of the test performed
	TEST	=	Physical test which will be described under comments
Information Code:	C	=	Client specified
	V	=	Vendor specified
	I	=	Information only
	SS	=	System Specification

General abbreviations used throughout the protocol include the following:

N/A	=	Not Applicable
N/AV	=	Not Available
N/S	=	Not Specified
IQ	=	Installation Qualification
P&ID	=	Process and Instrumentation Diagrams
RO	=	Reverse Osmosis
DI	=	Deionized
TEMP	=	Temperature

6 SYSTEM DESCRIPTION

XXX

7 OPERATIONAL QUALIFICATION TESTS

7.1 Loss of Power

Objective:

The objective of this test is to verify and document the action of the system to power failure and recovery during routine system operation.

Procedure:

While the system is in "Service" mode, remove power to the control panel. Wait for approximately two (2) seconds. Restore power and record the status of the system. Repeat this procedure for two (2) and ten (10) minutes intervals. Record the results.

References Required:

None.

Acceptance Criteria:

Upon power failure, all valves return to their "fail-safe" positions, and pumps XXX, XXX, and XXX shut down. Upon power being restored to the control panel, the system automatically returns to the service mode/cycle.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Reviewed By: _____ Date: _____ _____

7 OPERATIONAL QUALIFICATION TESTS (continued)

7.2 Alarms/Messages

Objective:

The objective of this test is to confirm that the associated system alarms are elicited as specified when an alarm condition is invoked and the appropriate system control response(s) is observed as specified.

Procedure:

Implement all associated system alarm conditions listed on the following test data sheets. The actual alarm condition should be introduced while the system is in the mode that the alarm is active. Each alarm condition should be evaluated in regard to its effect on the entire system control.

Due to the nature of alarm testing, the following approach will be used. All alarm conditions that can be physically created without potential for injury to personnel and/or damage to the equipment will be tested. In cases where there is potential for injury to personnel and/or damage to the equipment, alarm conditions will be simulated.

Create each alarm condition, observe, and document the alarms as well as the subsequent system control response(s). Document all references required. The following procedures may be used to create the alarm condition.

A1: Simulate the alarm using an electronic simulator.
A2: Change the set point.
A3: Trigger the alarm condition at the field device.
A4: Observe the alarm condition during the normal operation.
A5: Observe during input / output testing.
A6: Verified during FAT testing.

References Required:

XXX

Acceptance Criteria:

Once each alarm condition is created, the specified response, defined on the following test pages, will be observed. The alarms shall reset as specified.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Reviewed By: _____ Date: _____

7 OPERATIONAL QUALIFICATION TESTS (continued)

7.2 Alarms/Messages (continued)

Alarm/Condition Response Chart

Skid #	Tag #	Alarm Description	Delay (sec)	Expected Response	Procedure Utilized to Trigger Alarm	System Responds as Specified (Y/N)	Verified By/Date
XXX	XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX	XXX			
XXX	XXX	XXX	XXX	XXX			

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

7 OPERATIONAL QUALIFICATION TESTS (continued)

7.3 Operator Interface Tests

Objective:

The objective of this test is to verify the operation of devices on the control panel that actively interface with the control of the system.

Procedure:

Operate all switches, push buttons, indicators, and monitors/timers on the control panels. Verify that all switches, push buttons, indicators, and monitors/timers perform the functions specified for the RO/DI Water System. Document the results on the following test data sheets

References Required:

XXX

Acceptance Criteria:

All switches, push buttons, indicators, and controllers on the control panels perform the functions specified for the RO/DI Water System.

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

7 OPERATIONAL QUALIFICATION TESTS (continued)

7. 3 Operator Interface Tests (continued)

7.3.1 Control Panel Operation – Indicators

Control Panel Device/Description	Specified Function and Color	System Responds as Specified (Y/N)	Verified By/Date
RO Control Panel			
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
CDI Control System			
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		
XXX	XXX		

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

7 OPERATIONAL QUALIFICATION TESTS (continued)

7. 3 Operator Interface Tests (continued)

7.3.2 Control Panel Operation – Switches

Control Panel Device/Description	Specified Function	System Responds as Specified (Y/N)	Verified By/Date
RO System Control Panel			
XXX	XXX		
XXX	XXX		
XXX	XXX		
CDI System Panel			
XXX	XXX		
Distribution Pump Control Panel			
XXX	XXX		
XXX	XXX		
XXX	XXX		

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

7 OPERATIONAL QUALIFICATION TESTS (continued)

7. 3 Operator Interface Tests (continued)

7.3.3 Control Panel Operation – Push Buttons

Control Panel Device/Description	Specified Function	System Responds as Specified (Y/N)	Verified By/Date
CDI System Control Panel			
XXX	XXX		
RO System Control Panel			
XXX	XXX		

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

7 OPERATIONAL QUALIFICATION TESTS (continued)

7. 3 Operator Interface Tests (continued)

7.3.4 Control Panel Operation – Monitors/Timers

Control Panel Device/Description	Specified Function	System Responds as Specified (Y/N)	Verified By/Date
RO System Control Panel			
XXX	XXX		
XXX	XXX		
XXX	XXX		
CDI System Control Panel			
XXX	XXX		
XXX	XXX		
XXX	XXX		
Distribution Pump Control Panel			
XXX	XXX		

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

7 OPERATIONAL QUALIFICATION TESTS (continued)

7. 4 Sequence of Operations

Objective:

The objective of this test is to verify that the system responds as specified during the service mode of operation for the RO/DI system.

Procedure:

Observe the RO/DI system throughout the normal mode of operation. The following modes of operation are programmed into the ladder logic control system.

Service Mode

The systems may be observed during each of the operating modes by simulating events or changing the process variables. Operation of the RO/DI system must occur as specified in the system operation SOP and operation manuals for system. Observe the positions of the output devices during each distinct operating mode. Demonstrate that there were no changes to the software or that any changes to the software after the FAT was performed under a change control program and do not impact the sequencing of the system or the proper operation and position of the output devices. Demonstrate proper operation by observing the system through several sequences of various modes.

References Required:

XXX

Acceptance Criteria:

The system sequences through the modes as specified. Output devices respond as specified. All control responses are as specified in the following data sheets.

Acceptance Criteria Met: Yes ____ No ____ Initials/Date: _____

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

7 OPERATIONAL QUALIFICATION TESTS (continued)

7. 4 Sequence of Operations (continued)

Valve/Pump Sequence Chart

Step	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	Verified By/Date
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	
	O	O	O	O	O	O	O	O	O	O	O	O	

Notes:
1. XXX
2. X denotes fully open automatic valve or operating component that are on
   M denotes partially open valves
   O denotes fully closed valves or operating component that are off

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

8 OPERATIONAL QUALIFICATION DISPOSITION

Upon review of this executed protocol including certifications and other records (if applicable), the validation department is recommending to:

_____ Proceed with the Performance Qualification Exercise

_____ Other (Explain in Comments/ Observations/Conclusions)

(Refer to Summary Report)

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

9 OPERATIONAL QUALIFICATION APPROVALS

_____	_____
Engineering	Date
_____	_____
Validation	Date
_____	_____
Quality Assurance	Date

10 APPENDICES

10.1 Appendix I - Signature Identification Log Sheet

This log sheet is a record of each individual who signs or initials any page included in the Installation Qualification documents. Each person shall be identified by typed or printed name, full signature, and written initials, department represented (Quality Assurance, Engineering, Validation, Contractor, etc.).

NAME (type or print)	INITIALS	SIGNATURE	DEPARTMENT

10.2 Appendix II - Protocol Change Summary Sheet

Change Control /Deviation Number	Protocol Test No.	Protocol Page No.	Change Description/Comments	Verified By/Date

Reviewed By: _____ **Date:** _____

10.3 Appendix III - Test Instrumentation Calibration Certificates

Test Equipment Description	Manufacturer	Model No.	Serial No.	Protocol Test No.	Instrumentation Use	Calibration No.	Calibration Date	Calibration Due Date	Verified By/Date

Comments/Observations/Conclusions:

Reviewed By: _____ **Date:** _____

10.4 Appendix IV - Attachments

11.3 Appendix III – Phase One Protocol Study Manual Sample

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STUDY MANUAL FOR PROTOCOL NO. 002

A PHASE I SAFETY STUDY OF AUTOLOGOUS TRANSFECTED HUMAN FIBROBLASTS PRODUCING HUMAN FACTOR VIII IN PATIENTS WITH SEVERE HEMOPHILIA A

Study Sponsor:

Study Monitor:

1. STUDY PARTICIPANTS

1.1 Study sponsor

[illegible]

Mailing Address:

Contact:

Telephone:

Pager

Facsimile:

Contact

Telephone

Pager

Facsimile

1.2 Study monitor

Quintiles Incorporated

Mailing Address:

Telephone:

Facsimile:

Project Manager:

Telephone:

Facsimile

Site Monitor:

Telephone:

Facsimile

1.3 Clinical site

Site 007

Clinical Site:

Principal Investigators:

Telephone

Facsimile

Pager

Study Coordinator:

Telephone:

Facsimile:

Pager

2. STUDY METHODS

The clinical site may enter patients into the study after all regulatory documentation (notification of IRB approval of the study, appropriate Case Report Forms, Informed Consent Forms, a copy of the signed and dated protocol and a copy of the investigator's signed Form 1572) is available and on file at the clinical site. Patients will undergo a recruitment interview to determine eligibility for entry into the study. During the recruitment interview, the study will be explained to the patient and, if interested, the patient will be provided with an Informed Consent Form. As soon as the patient returns a signed Informed Consent Form, the patient will be enrolled in the study (refer to **Section 2.1** below). An entry physical examination, joint assessment, medical and medication history, clinical laboratory studies, and any other examinations or procedures required at the Baseline Evaluation will be performed to confirm eligibility.

2.1 Assignment of Patient ID Numbers

Upon enrollment of a patient in the study, clinical site personnel will assign the next sequential ten-digit Patient ID number to the patient. This Patient ID number consists of a three-digit pre-assigned **Protocol Number** (002 for this study) concatenated with a three-digit pre-assigned **Site Number** (007) concatenated with a four-digit sequential **Patient Number** (the first patient at each site is patient number 0001). For example, Patient ID Number 002-007-0003 indicates the third patient enrolled at the for this study. This number will be entered on all samples and information gathered for this patient for this study.

2.2 Treatment assignment

Patient identification numbers and dose groups will be assigned at the time the patient enrolls in the study. Three patients will be assigned to each of the four dose groups. The first three patients, Group 1, will be assigned to receive 100 x100^6 transfected autologous fibroblasts administered in the greater omentum. Patients in Group 2, will receive 400 x 100^6 transfected fibroblasts, administered in the greater omentum. Patients in Group 3 and Group 4 will receive 100 x 100^6 and 400 x 100^6 transfected fibroblasts, respectively, administered in the omental bursa (lesser sac).

Patients will not be treated at an advanced dose group until all patients at the previous dose group have been observed for at least 6 weeks following the autologous fibroblast implantation. At least one patient with serological evidence of HIV infection, and one patient without serological evidence of HIV infection will be included in each group.

Dose Group and Treatment Assignment Schedule

Group	Number of patients	Implantation Site	Number of hFVIII-expressing autologous fibroblasts
Group 1	3	Greater omentum	100×10^6
Group 2	3	Greater omentum	400×10^6
Group 3	3	Omental bursa (lesser sac)	100×10^6
Group 4	3	Omental bursa (lesser sac)	400×10^6

2.3 Assignment of replacement Patient ID Numbers

If a patient drops out, or withdraws from the study prior to completion of the week 12 visit, it is important that a new patient be entered at the same dose level and treatment group assignment. Consequently, if a patient drops out, or withdraws prior to completion of the 12 week visit, it is imperative that the clinical site personnel immediately notify the sponsor, , or his designate, Clinical Affairs, should be contacted at to report the patient's information including: patient ID number, initials, dose level, and treatment group of the subject who has dropped out, or who has been withdrawn from the study.

The clinical site will be informed that they must call prior to assigning a new Patient ID Number to the next patient they enroll. The first patient to enroll, following the withdrawal of another subject, will be given a replacement Patient ID Number assignment in place of the next sequential Patient ID Number. Replacement Patient ID Numbers also consist of the protocol number (002) concatenated with the clinical site number (007) concatenated with a sequential a four digit Patient Number. However, this patient number will be 0020 or higher.

The patient with the replacement Patient ID Number will receive the same dosage level and treatment randomization assignment as the patient who dropped out, or withdrew from the study.

2.4 Collection and preparation of clinical laboratory specimens

will serve as the for this study. will supply a separate manual for the collection and preparation of clinical specimens. Please refer to the Clinical Trials Center, Clinical Investigation Manual for any questions regarding the collection, preparation and shipment of clinical laboratory specimens.

Pre-packaged, visit specific supplies and requisitions will be supplied to the clinical site for the collection and shipment of clinical specimens. A courier will pick-up specimens from the site 6 days a week. There is no courier service on Sundays.

At the Baseline Evaluation, and study visits Day -1 through Day 6, certain clinical laboratory specimens will be collected for analysis at the site's clinical laboratory facilities. These tests will be analyzed at the in order to supply the investigator with same day results to be

utilized in making therapeutic decisions regarding the adjustment of the patients factor VIII replacement therapy dose. In addition several other tests requiring same day results will be drawn pre-operatively and to determine if the patient is hemodynamically stable prior to discharge.

Clinical Laboratory Specimens to be Analyzed at BIDMC

Study Visit	Name of Tests	Number of Specimens Required
Baseline Evaluation	hFVIII activity level (for FVIII Clearance Testing)	3 hFVIII activity levels
Day -1 (Pre-Op)	CBC/diff./platelet count PT/aPTT hFVIII activity level; ABO group and Rh type Serum electrolytes Chemistry panel	1 each
Day 0 (Implant)	CBC/diff./platelet count PT/aPTT hFVIII activity level;	1 each
Day 1 (Discharge)	CBC/diff./platelet count PT/aPTT hFVIII activity level; ABO group and Rh type Serum electrolytes Chemistry panel	1 each
Day 2 through 6	hFVIII activity level	1 daily

Clinical site personnel should speak directly with the institution's clinical laboratory to determine specimen requirements for these laboratory studies.

Specimens for Cytotoxic Lymphocyte (CTL) Assay

These specimens will be collected at baseline (prior to implantation of autologous transfected fibroblasts producing human factor VIII) and at 1, 3, 6, 12, 18, and 24 months following the procedure. For the CTL specimen, 10 mL of blood must be collected in a sodium heparin container (green top), maintained at room temperature, and delivered to within 24 hours of the time of collection. The medical monitor ( ) should be paged ( ) at the time of CTL specimen collection.

2.5 Collection and preparation of skin biopsy for shipment

As soon as the patient's eligibility for entry into the study is confirmed, the clinical site personnel must contact the general surgeon or dermatologist to schedule the patient's skin biopsy procedure. The site must relay schedule information to or his designate, Clinical Affairs, at will be responsible to make arrangements for the biopsy specimen to be collected from the clinical site and delivered to s pilot manufacturing facility.

Following confirmation of the patient's eligibility, he will undergo a biopsy of unexposed skin, which will be performed by the surgical subinvestigator participating in the study (refer to the clinical protocol for a copy of the skin biopsy procedure).

When taken, the biopsy specimen will be placed into a specimen container, containing transport medium, provided to the clinical site by in a Biopsy Kit (refer to **Appendix A** for a copy of the **Biopsy Kit Directions for Use**).

If a representative is not standing-by to take the packaged biopsy specimen, immediately notify or his designate, Clinical Affairs, at (pager) that a biopsy is waiting for transport. Do not freeze the specimen. The closed Biopsy/Excision Kit may be stored in a refrigerator while awaiting pick-up by . If a representative has not picked-up the package within two hours of packing, contact again.

2.6 Study material preparation at TKT

At s pilot manufacturing facility, dermal fibroblasts will be isolated by enzymatic digestion of the biopsy specimen. The fibroblasts will be expanded briefly in cell culture and then transfected by electroporation with genes encoding human factor VIII (hFVIII) and neomycin resistance. Fibroblasts expressing hFVIII will be selected and cloned, and one fibroblast clone will be chosen for implantation. This production clone will then be propagated until the required number of fibroblasts are obtained.

This process, from receipt of biopsy specimen to packaging of transfected fibroblasts, requires approximately six to eight weeks.

or his designate, Clinical Affairs, will notify the clinical site personnel approximately one week in advance that the transfected fibroblasts will be available for implantation. At this time, the site must contact the patient and general surgeon to schedule the implantation visit, study visit Week 0. or another Clinical Affairs representative will confirm the delivery schedule one to two days prior to the shipment of the study material.

2.7 Study material packaging

Transfected fibroblasts will be adjusted to the appropriate cell number in phosphate-buffered saline, and placed into a sealed syringe. The syringe containing the hFVIII-transfected fibroblasts will be labeled and individually sealed in a labeled plastic pouch. The syringe in the

pouch is placed in an inner Styrofoam box with foam padding. This inner Styrofoam box, along with two ice packs, will be placed into an outer Styrofoam box which is inside a shipping box.

2.8 Study material labeling

The syringe and/or pouch will be labeled with; the protocol number: the ten-digit Patient ID Number; the patient's initials; the time and date of release of the product by s Quality Assurance staff; the sponsor/manufacturer's information; the manufacturing lot number; a statement about the autologous nature of this product, that the entire syringe contents are to be administered and the storage requirements; and the statement: "**Caution: New Biologic Drug — Limited by Federal Law to Investigational Use**".

2.9 Receipt of study material

The clinical site personnel will receive hFVIII-transfected fibroblasts directly from a representative. The shipping box containing the fibroblasts will be transported directly from the pilot manufacturing facility at to the clinical site just prior to the time of the implantation procedure.

A member of the study team must receive the study material from the . representative. Upon receipt, be sure to complete the information required in the appropriate area of the form entitled **Clinical Protocol No. 002: Clinical Study Material Delivery, Receiving, and Disposition of Syringe Record** (refer to **Appendix C** for a copy of this form). Transfected fibroblasts should be implanted as soon as possible, but no later than the time of expiration indicated on the above form. If implantation is not performed immediately, store the box in a cool, secure location.

2.10 Study material administration

Dosing will consist of laparoscopic implantation of the transfected autologous fibroblasts into the patient's greater omentum or omental bursa. The volume of fibroblasts to be injected will range from approximately 1 to 8 mL . Fibroblasts will be injected during the laparoscopic procedure using the syringe in which they arrived.

Prior to implantation, the cells in the syringe must be resuspended according to the **Clinical Protocol 002: Procedure for Resuspending Cells** (refer to **Appendix D** for a copy of this procedure). The procedure is summarized below:

1. If you have not already done so, unpack the transport box and remove the inner Styrofoam box containing the syringe for injection. Retain all packing materials. Verify that the Patient ID number on the syringe and pouch matches that of the patient to be implanted.
2. Each syringe is individually packaged within a clear sealed pouch. Hold the pouch up to the light and observe the contents. The syringe will be capped with a black stopper on the tip, and will have a flexible plastic collar around the plunger to prevent the plunger from moving. **DO NOT REMOVE THE SYRINGE FROM THE POUCH, AND DO NOT REMOVE THE BLACK STOPPER OR THE PLASTIC COLLAR.**
    - During transport, the cells should have settled into a pellet against the barrel and/or plunger of the syringe. If you note any unusual observations (*e.g.* moisture in the pouch,

cracks in the syringe barrel, missing collar, warm to the touch, etc.), contact Clinical and Regulatory Affairs, at

3. Leaving the syringe in the pouch, flick the barrel of the syringe in the area where the cells have settled, until the cells completely detach from the syringe wall. Be careful not to flick your finger too close to the black stopper. Now invert the syringe 10 times.
4. Place the pouch containing the syringe on the nutator rotating platform on its long axis using one or two rubber bands to hold the pouch in place (keep the rubber bands away form the plastic collar on the plunger).
5. Allow the platform to rock for 10 minutes.
6. Turn off the nutator and remove the pouch containing the syringe. Hold the pouch up to the light and observe the contents of the syringe. When the cells are completely and uniformly resuspended, the contents of syringe will have an opalescent appearance with no obvious cell clumps.
7. If you observe clumps, flick the barrel and invert the syringe several more times until the appearance of the contents of the syringe is uniform.
8. If necessary, repeat steps 3-7 until the desired uniform consistency is obtained. **DO NOT PROCEED BEYOND THIS STEP UNTIL ALL VISIBLE CLUMPS ARE DISPERSED.**
9. Remove the syringe from the pouch. The flexible plastic collar around the syringe plunger is slit along its long axis. Open the collar at this lengthwise slit and carefully remove the collar from the syringe plunger. The syringe is now ready for implantation.

2.11 Syringe disposition

Follow the directions on the **Clinical Protocol No. 002: Clinical Study Material Delivery, Receiving, and Disposition of Syringe Record (Appendix C)** form for disposing of empty syringes. If syringe containing the autologous fibroblast product is not used, or if the syringe is partially used, the syringe must be returned to TKT immediately. In this event, please contact or his designate, Clinical Affairs at immediately.

2.12 Study material storage at the clinical study site

Study material will be transported directly from the pilot manufacturing facility at to the clinical site at the time of the implantation procedure. The study material must be implanted as soon as possible after receipt, and should be stored at 2–8°C (36–46°F) until implantation. Study material expiration time will be indicated on the form entitled **Clinical Protocol No. 002: Clinical Study Material Delivery, Receiving, and Disposition of Syringe Record (Appendix C)**. If the implantation cannot be completed prior to the time indicated for expiration, contact or his designate, Clinical Affairs at immediately.

2.13 Study material accountability

The Food and Drug Administration (FDA) requires a patient-by-patient accounting of the disposition of all investigational study material received by the clinical site. Records of study material disposition required by federal regulation include the date received by the clinical site,

date administered, quantity administered, and the patient to whom the study material was administered. The principal investigator is responsible for the accountability of all used and all unused study material and containers.

The clinical site should use an Investigational Test Material Accountability Record to document study material disposition. **Appendix B** of this manual includes a sample **Clinical Study No. 002: Clinical Study Material Accountability Log** form with instructions. All items on the form must be completed in full. The Quintiles Site Monitor must approve the area where clinical site personnel will maintain the study material accountability records.

3. ADVERSE EXPERIENCES

3.1 Definition of adverse experience

An adverse experience is any noxious, pathologic, or unintended change in anatomical, physiologic, or metabolic function as indicated by physical signs, symptoms, and/or laboratory changes occurring in any phase of a clinical trial, whether associated with study material and whether or not considered study material-related. This includes an exacerbation of a pre-existing condition or the significant failure of expected pharmacologic action.

Adverse experiences include:

- Worsening (change in nature, severity, or frequency) of conditions present at the onset of the study;
- Intercurrent illnesses;
- Drug interactions;
- Events related or possibly related to concomitant medications;
- Abnormal laboratory values (this includes significant shifts from baseline within the range of normal that the investigator considers to be clinically important); and,
- Clinically significant abnormalities in physical examination, vital signs, weight, electrocardiogram, and chest X–ray.

3.2 Recording adverse experiences

All adverse experiences, regardless of relationship to study material, must be recorded on the **Adverse Event Record (Form 2.34)** and/or **Serious Adverse Event Record (Form 2.35)** case report forms. All adverse experience reports should contain the date the adverse experience occurred, a brief description of the event, the time of onset, the duration of event, the severity, the treatment required, the presumed relationship to study material, the action taken, the outcome, and whether the event is classified as serious. The relationship to study material and the severity/intensity of each adverse experience must be recorded as described in **Sections 3.2.1 and 3.2.2.**

The investigator should treat patients with adverse experiences appropriately and observe them at suitable intervals until the events resolve. Adverse experiences may be discovered through the following means:

- Observation of the patient;
- Questioning of the patient;
- Complaint by the patient; or,
- Abnormal clinical laboratory values, chest X–ray, or ECG.

Patients should be asked "How do you feel?" and further questions should follow if there are indications of an adverse experience. The questioning should be conducted with due regard for objectivity and, in particular, the questioner should gather information about adverse experiences

from questioning the patient, spontaneous report by the patient, laboratory reports (including ECG and chest X–ray) and clinician's observations.

Adverse experiences may also include laboratory values which become significantly out-of-range. In the event of an out-of range value, the laboratory test should be repeated until it returns to normal or can be explained and the patient's safety is not at risk.

3.2.1 Relationship to study material

The investigator must assess the relationship of each adverse experience to study treatment and record the assessment on the **Adverse Event Record (Form 2.34)**, and/or **Serious Adverse Event Record (Form 2.35)** case report forms.

The investigator should consider the following criteria when assessing the relationship between an adverse experience and the study material:

- The temporal sequence of the medical event occurrence and study material administration;
- Improvement of the adverse experience with discontinuation of study material; and,
- Consistency with the patient's clinical state or with other concurrent therapies.

The relationship of each adverse experience to study material must be recorded as one of the choices on the scale below:

Not Related	Unrelated to study material;
Possibly Related	Unlikely relationship to study material, but cannot rule out relationship with certainty;
Probably Related	Relationship to study material is fairly certain;
Definitely Related	Relationship to study material is certain; or,
Unknown	Relationship to study material is unknown.

3.2.2 Severity

The investigator must assess the severity of each adverse experience and record the assessment on the **Adverse Event Record (Form 2.34** and/or **Serious Adverse Event Record (Form 2.35)** case report forms.

The severity of each adverse experience must be recorded on the **Adverse Event Record (Form 2.34** and/or **Serious Adverse Event Record (Form 2.35)** case report forms, as one of the choices on the scale below:

Mild	No limitation of usual activities;
Moderate	Some limitation of usual activities;
Severe	Inability to carry out usual activities; or,
Life-Threatening	Immediate risk of death.

A life-threatening adverse experience is defined as an adverse experience during which the patient was, in the view of the investigator, at immediate risk of death from the

experience as it occurred. This definition does not include an experience that, had it occurred in a more severe form, might have caused death.

3.3 Unexpected adverse experiences

Federal regulation defines an unexpected adverse experience as any adverse experience, the specificity or severity of which is not consistent with the current Investigator Brochure. If an Investigator Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thrombo-embolism and cerebral vaculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (*e.g.*, included in the Investigator Brochure) rather that from the perspective of such experience not being anticipated of the pharmacological properties of the pharmaceutical product. The investigator must list all unexpected adverse experiences on the **Adverse Event Record (Form 2.34), Adverse Event Two Year Follow-Up (Form 3.36)** and/or **Serious Adverse Event Record (Form 2.35)** case report forms.

Because adverse experience information is not available for fibroblasts expressing hFVIII, the information included in the Investigator Brochure is based on theoretical considerations and previous clinical experience with conventional hFVIII replacement therapy and laparoscopic procedures. The mature protein secreted by fibroblasts transfected with the hFVIII gene is, to the best of 's knowledge, equivalent to the naturally occurring hFVIII.

3.4 Serious adverse drug experiences

Federal regulation defines a serious adverse experience (event) or reaction as any untoward medical occurrence, at any dose, that results in any of the following outcomes:

- **Results in death,**

Federal regulation defines a fatal adverse experience as any death that occurs during the conduct of a clinical trial, including deaths which appear to be completely unrelated to study therapy (*e.g.*. car accident). If a patient dies during the study, and an autopsy is performed, autopsy results will become part of this patient's case report form. Possible evidence of organ toxicity and the potential relationship of the toxicity to the study material will be of particular interest. The autopsy report should distinguish the relationship between the underlying diseases, their side effects, and the cause of death.

- **Is life-threatening,**

Federal regulation defines a life-threatening adverse drug experience as any adverse drug experience that places the patient or subject, in view of the investigator, at immediate risk of death from the reaction as it occurred. This definition does not include an event that, had it occurred in a more serve form, might have caused death.

- **Requires inpatient hospitalization or prolongation of existing hospitalization,**

- **Results in a persistent or significant disability/incapacity, or**
- **Is a congenital anomaly/birth defect.**

Further, an important medical event, defined as any medical event that may or may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse drug experience when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. For example, all of the following should be considered serious adverse events: allergic bronchospasm requiring intensive treatment in any emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

3.5 How to report serious adverse drug experiences

All adverse experiences must be recorded on the **Adverse Event Record (. Form 2.34** and/or **Serious Adverse Event Record (Form 2.35)** case report forms. The investigator must also immediately report any serious or unexpected drug adverse experience which occurs between the time the patient enters the study throughout the entire 2 year course of the study to Medical Monitor, , at during business hours. If is not available, or if you are calling outside business hours, please page t All deaths and life-threatening adverse experiences should be reported to the Medical Monitor within 24 hours of discovery of the event. When calling to report a serious adverse experience, state that you are reporting a medical emergency and give the principal investigator's name, your name, the telephone number where you can be reached, and the protocol number and title (002, "A Phase I Safety Study of Autologous Transfected Human Fibroblasts Producing Human Factor VIII in Patients with Severe Hemophilia A").

MEDICAL MONITOR:

Vice President Clinical and Regulatory Affairs

Telephone:
Facsimile:
Pager:

If calling after business hours, please use page number.

If , is not available contact the following personnel:

Director Clinical Affairs

Telephone:
Facsimile:
Pager:

If calling after business hours, please use page number.

During the initial phone call, the Medical Monitor will require the following information about the patient:

- Patient identification including Patient ID Number, initials, and sex;
- Date of study material implantation.
- Study material dosage level.
- Date, duration, and description of adverse experience;
- Action taken;
- Concomitant therapy (including doses, routes, and regimens);
- Pertinent laboratory data;
- Medical history (including time on study prior to adverse experience, time post-biopsy, and time post-implant).

In addition to the above information, the Medical Monitor will require the investigator's assessment of the following:

- Severity of the adverse experience;
- Relationship of the adverse experience to the study material; and,
- Outcome of the adverse experience **Adverse Event Record (Form 2.34** and/or **Serious Adverse Event Record (Form 2.35)** case report forms. This may be completed prior to contacting to assist in relaying required information. After telephoning , the **Serious Adverse Event Record (Form 2.35)** case report form, containing as much information as is available at that time, should be sent via facsimile to the Medical Monitor, . The principal investigator must also submit substantiating data in hard copy form, such as diagnostic test reports, to the Medical Monitor as soon as possible.

The principal investigator and the sponsor or the sponsor's designee will review and evaluate each serious adverse event report, and assess the relationship of the adverse event to study material and to underlying disease.

The principal investigator and sponsor will determine the need for further action based on their assessment of the serious adverse experience. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical trial. If the discovery of a new adverse experience related to study material raises concern over the safety of continued administration of the study material to patients, will take immediate steps to notify all investigators participating in this clinical trial and the FDA.

Further action that may be required includes the following:

- Alteration of existing research by modification of the protocol;
- Discontinuation or suspension of the study;
- Alteration of the informed consent process by modification of the existing consent form and informing current study participants of new findings; and,
- Modification of previously identified expected adverse experiences to include adverse experiences newly identified as study material-related.

3.6 Reporting safety information to the Institutional Review Board (IRB)

The investigator must promptly report to the Medical Monitor, at or pager number , and her/his Institutional Review Board (IRB) all unanticipated problems involving risks to human subjects. This includes death from any cause and all serious adverse experiences. Documentation of IRB notification should be mailed to TKT within three days.

3.7 Protocol deviations due to an emergency or adverse experience

Departures from the protocol will be determined as allowable on a case-by-case basis only in the event of an emergency. The investigator or other physician in attendance in such an emergency situation must contact the Medical Monitor, at or pager number

Such contacts with will be made as soon as possible to permit a decision as to whether or not the patient, for whom the departure from the protocol was effected, is to continue in the study.

3.8 Follow-up of adverse experiences

All adverse experiences should be followed until they are resolved. All serious adverse experiences and those non-serious events assessed by the investigator as possibly related to the investigational medication should continue to be followed even after the patient's participation in the study is over. Such events should be followed until they resolve or until the investigator assesses them as chronic or stable.

3.9 Withdrawal from the study due to adverse experiences

Patients withdrawn from the study due to any adverse experience must be followed by the investigator until the outcome is determined; additional reports must be provided when requested.

Adverse experiences for which a patient may be withdrawn from the study include:

- Intercurrent illnesses which may affect significantly the patient's response to study material or the assessment of the patient's clinical status; and,
- Side effects which would jeopardize the patient's safety or obscure the effects of the study material.

4. GUIDELINES FOR COMPLETING THE CASE REPORT FORMS

4.1 Introduction

The following guidelines pertain to the completion of the case report forms (CRFs) for Protocol Number 002. Please review these guidelines carefully, and refer to them as you complete the CRFs for this study.

These guidelines provide general as well as specific instructions for the completion of CRFs for this study. However, they are to be used as an aid and are not intended to be used for study clarification. Refer to the protocol for such information.

Should questions or problems arise during the course of the study, please contact a Quintiles Site Monitor. Your Quintiles Site Monitor is available to you to answer any study-related questions you might have. A list of the Quintiles Site Monitor and Project Managers, with telephone and facsimile numbers, is located in **Section 1** of this manual for reference.

Schedule of protocol events (continued)

Evaluations	Wk -7	Day -1	Day 0	Day 1	Day 2-6	Wk 1	Wk 2,3	Wk 4	Wk 6,8	Wk 12	Wk 18	Mos 6,12 18,24
vWF ristocetin co-factor	●	●				●	●	●	●	●	●	●
vWF antigenic	●	●				●	●	●	●	●	●	●
ABO group and Rh type		●										
Serum electrolytes[b]	●	●		●		●				●		●
Chemistry panel[c]	●	●		●		●				●		●
Urinalysis	●					●				●		●
Blood for CTL assay	●							●		●		●
Peripheral CD4 counts	●							●		●		●
Viral testing[d]	●											●
Skin biopsy	●											
Post-biopsy tel. interview[e]	●											
Fibroblast implant			●									
Hospital admission			●									
Hospital discharge				●								

[a]Determined from patient diary records (except for study day 1, when data will be determined from in-patient medical records)

[b]Serum electrolytes include the following:

Sodium
Potassium
Chloride
Total carbon dioxide

[c]Chemistry panel includes the following:

Serum glucose
Serum total calcium
Serum total protein
Serum albumin
Serum creatinine
Serum urea nitrogen
Serum total bilirubin
Serum alkaline phosphatase
Serum alanine aminotransferase
Serum aspartate aminotransferase
Serum lactate dehydrogenase
Serum gammaglutamyltransferase
Serum creatine phosphokinase
Serum amylase
Serum lipase
Serum triglycerides
Serum cholesterol

[d]Viral testing includes the following:

Hepatitis A antibody
Hepatitis B surface antigen
Hepatitis C antibody
HIV antibody

[e]Post-biopsy telephone interview: Patient will be called 24 hours and 7 days following the skin biopsy.

4.3 General guidelines for completing the case report forms

Listed below are general instructions that apply to the completion of every case report form for this study:

- All forms must be neatly filled out using a ball-point pen with dark ink or typed using dark ink. Do not use correction fluid at any time. If you make an error, cross out the error with a single horizontal line, clearly record the new information next to the error, and initial and date the correction. For example:

  Hematocrit: ~~29.6%~~ **39.5%** *adh* *10/24/94*

- Use lead and end zeros when necessary to complete all boxes. For example:

  Weight (kg): | **0** | **5** | **0** |

- Avoid using abbreviations when completing the CRFs.
- All spaces on the case report forms should be completed except where stated otherwise. If the information is not applicable or not done, it is acceptable to record NA or ND, respectively. If part of a date or parameter is unknown, **UNK** should be recorded (*e.g.*, if only the year is known, the date should be recorded as **UNK/UNK/94**).
- Comment only in designated spaces on the case report forms. Do not comment outside the boxes. If there are comments and no space is provided or there are additional comments that do not fit in the designated space, please enter the information and date the entry on a Comments form (**Form Q**) according to the instructions in this section.
- The date should be entered using two-digit numbers to represent the month, day, and year. For example: **05/21/94**

4.4 Header information

The right area of the header is identically laid out on all case report forms for Protocol Number 002. The following information is pre-coded on the case report forms:

- **Patient ID Number** consisting of:
  (1) Protocol Number — a three-digit pre-assigned number (002 for this study)
  (2) Clinical Site Number — a three-digit pre-assigned number
  (3) Patient Number — a four-digit sequentially assigned number

This 10–digit Patient ID Number (###-###-####) has already been entered on these forms by Before you enter any information on a case report form, verify that this number corresponds with that of the patient whose data you wish to record.

Record the following additional information on each form:

- **Patient Initials:** Record the patient's first, middle, and last initials in the space provided (*e.g.*, X Y Z). If no middle initial is available, draw a horizontal line through the box (*e.g.*, X— Z).
- **Date:** Record the date in the space provided. The month, day, and year should be entered as two-digit numbers (*e.g.*, for January 20, 1999 the correct entry should be 01/20/99). A complete date must be recorded.

5. REGULATORY CONSIDERATIONS

5.1 Protection of human subjects and informed consent

No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator may seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information given to the subject or the representative must be in a language understandable to the subject or the representative. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Each prospective study patient or the legal guardian of each prospective study patient must be informed of the purpose and the nature of the study, its possible hazards and benefits, and the patient's right to withdraw from the study at any time without prejudice to further treatment.

Each patient must give written informed consent to the investigator prior to initiation of any screening assessments specifically for this study.

Signed consent forms must remain in the patient's file and must be available for verification by a representative of the sponsor.

5.2 Assurance of institutional review

A clinical trial may not be initiated unless the proposed investigation has been reviewed and approved by, and remains subject to continuing review by, an Institutional Review Board (IRB) meeting federal regulations. will not initiate a clinical site until written approval from the clinical site's IRB has been received by .

The principal investigator is responsible for assuring initial and continuing review and approval of the clinical study by the IRB at his or her site. The investigator must also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in research without IRB approval, except where necessary to eliminate apparent hazards to human subjects. If the study remains in progress for more than one year, annual renewal and re-approval from the IRB must be obtained. Documentation of renewal must be submitted to Quintiles. For any new investigators added during the conduct of the study, a signed Form FDA 1572 "Statement of Investigator" must be filed with Quintiles referencing the change.

5.3 Investigator responsibilities

The following summary was abstracted from the Code of Federal Regulations. A complete copy of the relevant CFR and ICH guidelines will be provided to the investigator by .

Federal regulation states that the investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement (Form FDA 1572), the investigational plan (protocol), and all applicable regulations, for protecting the rights, safety, and welfare of subjects under the investigator's care, and for the control of material under investigation.

Investigators must complete and sign a Form FDA 1572 before they may participate in the clinical investigation. Signing this form means that the investigator agrees to:

- Conduct the study(ies) in accordance with relevant, current protocol(s) and only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of patients;
- Comply with all regulations covering obligations of clinical investigators;
- Personally conduct or supervise the investigation(s);
- Inform patients that the study material is used for investigational purposes and ensure that regulations regarding Informed Consent and IRB approval are met;
- Report to the sponsor adverse experiences that occur during the course of the investigation;
- Read and understand the investigator's brochure, including potential risks and side effects of the study material; and,
- Ensure that all personnel assisting in the conduct of the study are informed about their obligations in meeting these commitments.

Additional responsibilities of the investigator are detailed in subsequent sections of this manual.

5.4 Failure to meet investigator responsibilities

The investigator must protect the integrity of the data collected in the clinical trial by adhering to the responsibilities outlined in this manual. The statistical power and clarity of the data are maintained by eliminating bias, false data, and error.

In order to ensure the successful completion of the clinical trial, the FDA requires the investigator to meet all requirements outlined in Subpart D, § 312.50 through § 312.70 of the Code of Federal Regulations. The FDA routinely audits clinical sites to ensure that investigators adhere to the Code of Federal Regulations. The table below presents a summary of findings of routine FDA audits of clinical sites.

Failure of the investigator to follow the Code of Federal Regulations may result in any of the following consequences:

- Invalidation of the clinical study conducted by the investigator;
- Delayed or disapproved marketing authorization application;
- Disqualification of the clinical investigator;
- Restrictions put on the investigator; and,
- Criminal charges.

Results of FDA Routine Data Audits of Clinical Investigators

	July 1981 to September 1983 N(%)	October 1983 to September 1985 N(%)	October 1985 to April 1988 N(%)
Routine data audits	415 (100%)	422 (100%)	569 (100%)
Specific deficiencies:			
Problems with patient consent	253 (61%)	246 (58%)	291 (51%)
Inadequate drug accountability	143 (34%)	91 (22%)	88 (15%)
Protocol nonadherence	114 (27%)	132 (31%)	155 (27%)
Inaccurate records	91 (22%)	96 (23%)	131 (23%)
Records not available	17 (4%)	8 (2%)	14 (2%)
Miscellaneous deficiencies	93 (22%)	153 (36%)	168 (30%)

Abstracted from the *Journal of the American Medical Association*, May 5, 1989 (Vol. 261, No. 17, p. 2507).

5.5 Informed consent

Before initiation of the study, the investigator must provide ' with a copy of the IRB approved consent form, typed on the appropriate (investigator, clinic, or hospital's) letterhead. Prior to study entry, a copy of the consent form must be given to the patient or the patient's guardian signing the consent form, and the signed form returned to the investigator. An investigator must obtain the informed consent of each human subject to whom the study material is administered. The primary investigator or sub-investigator listed on the Form FDA 1572 may sign as the physician.

A model informed consent form, which incorporates all required elements of informed consent, appears in **Appendix C** of the protocol.

5.6 Control of the study material

An investigator agrees to administer the study material only to patients under his or her personal supervision, or the supervision of a sub-investigator who is listed on Form FDA 1572. The investigator will not supply the study material to any person not authorized to receive it under the regulations.

5.7 Investigator reports

5.7.1 Progress reports

The investigator must provide all reports to the sponsor of the study material. The sponsor is responsible for collecting and evaluating the results obtained from the clinical investigations of its study material. The sponsor is required by federal regulation to submit annual reports to the FDA on the progress of its investigations.

5.7.2 Safety reports

The investigator must report promptly to the sponsor any adverse experience that may reasonably be regarded as caused by, or probably caused by, the study material. If the adverse experience is alarming, the investigator must report the adverse experience to the sponsor immediately.

NOTE: Instructions for reporting adverse experiences are described in **Section** 3 of this Manual.

5.7.3 Final report

The investigator must provide the sponsor with an adequate final report shortly after completion of the investigator's participation in the clinical trial.

5.8 Assurance of IRB review

The investigator must assure that an IRB that complies with federal regulations will be responsible for the initial and continuing review and approval of the proposed clinical study. The written, signed approval must contain specific identification of the documents approved (*i.e.*, the investigator's name, the protocol title and/or protocol number, the date of the protocol, and the informed consent).

The investigator must also assure that he or she will report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

5.9 Inspection of investigator's records and reports

The investigator must, upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

5.10 Investigator record keeping and record retention

5.10.1 Disposition of study material

The investigator must maintain accurate records demonstrating date and amount of study material received, to whom dispensed (patient-by-patient accounting), and accounts of any study material accidentally or deliberately destroyed.

5.10.2 Case histories

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational study material. All information recorded on the case report forms for this study must be identical to the patient's source documentation (*i.e.*, medical records).

5.10.3 Record retention

All required records must be maintained by the investigator for two years following the date a marketing application is approved for the study material or, if no application is filed or the application is not approved, for two years after the investigation is discontinued and the FDA is notified.

At the administrative office of each clinical site, complete, accurate, and current study records must be maintained. Federal regulation requires that a copy of records (*e.g.*, informed consent, laboratory reports, case report form copies, source documents, study material dispensing records) which support case report forms of this study must be retained in the files of the responsible investigator. These must be retained for a minimum of two years following notification that the application for marketing authorization has been withdrawn or the study material has been approved.

Study records include all of the following:

1. Patient Records:
   a. Signed informed consent form;
   b. Source documents: progress notes, laboratory reports, *etc.*; and,
   c. Case report forms (copies).
2. Study Material Audit Records:
   a. Receipt;
   b. Dispensing; and,
   c. Return to sponsor.
3. Administrative files including all documents, reports, and correspondence relating to the study. These include IRB, sponsor, medical monitor, and clinical monitor correspondence.

During the conduct of the study, Quintiles' monitoring staff will inspect these records at scheduled clinical site visits to ensure compliance with FDA Guidelines and Good

Clinical Practice. Missing records will be brought to the attention of the investigator and/or the study coordinator for immediate follow-up.

5.11 Transfer of responsibility

In the event that the principal investigator relocates to an alternate clinical location following completion of the study, but during the required time period for retention and maintenance of study records, the principal investigator must make arrangements for maintenance of study records at the clinical site. Additionally, the investigator must notify Quintiles of the change, and of the location where the records will be maintained.

5.12 Important obligations not specific to investigators — safety reports

Completion and filing of the IND Safety Report is the obligation of the sponsor, but the investigator can be prosecuted for failing to forward safety information to the sponsor.

Any serious and unexpected adverse reaction "associated with the use of the study material" must be reported to the FDA in a written safety report no later than 15 calendar days after the sponsor's initial receipt of the information.

ANY UNEXPECTED FATAL OR LIFE-THREATENING EVENTS ASSOCIATED WITH THE USE OF THE MATERIAL MUST BE REPORTED TO THE FDA BY TELEPHONE NO LATER THAN 7 CALENDAR DAYS AFTER THE INITIAL RECEIPT OF THE INFORMATION.

5.13 Title 21 Code of Federal Regulations §§ 312.60-70: Responsibilities of Investigators

§ 312.60 General responsibilities of investigators.

An investigator is responsible for ensuring that an investigation is conducted according to the protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. An investigator shall, in accordance with the provisions of Part 50, obtain the informed consent of each human subject to whom the drug is administered, except as provided in § 50.23. Additional specific responsibilities of clinical investigators are set forth in this part and in Parts 50 and 56.

§ 312.61 Control of the investigational drug.

An investigator shall administer the drug only to subjects under the investigator's personal supervision or under the supervision of a sub investigator responsible to the investigator. The investigator shall not supply the investigational drug to any person not authorized under this part to receive it.

§ 312.62 Investigator record keeping and record retention.

(a) Disposition of drug. An investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects. If the investigation is terminated, suspended, discontinued, or completed, the investigator shall return the unused

supplies of the drug to the sponsor, or otherwise provide for disposition of the unused supplies of the drug under § 312.59.

(b) Case histories. An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational drug or employed as a control in the investigation.

(c) Record retention. An investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910-0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§ 312.64 Investigator reports.

(a) Progress reports. The investigator shall furnish all reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained. The sponsor is required under § 312.33 to submit annual reports to FDA on the progress of the clinical investigations.

(b) Safety reports. An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.

(c) Final report. An investigator shall provide the sponsor with an adequate report shortly after completion of the investigator's participation in the investigation.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§ 312.66 Assurance of IRB review.

An investigator shall assure that an IRB that complies with the requirements set forth in Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987]

§ 312.68 Inspection of investigator's records and reports.

An investigator shall upon request from any properly authorized officer or employee of FDA, at reasonable times, permit such officer or employee to have access to, and copy and verify any records or reports made by the investigator pursuant to § 312.62. The investigator is not required to divulge subject names unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual case studies, or do not represent actual results obtained.

§ 312.69 Handling of controlled substances.

If the investigational drug is subject to the Controlled Substances Act, the investigator shall take adequate precautions, including storage of the investigational drug in a securely locked, substantially constructed cabinet, or other securely locked, substantially constructed enclosure, access to which is limited, to prevent theft or diversion of the substance into illegal channels of distribution.

§ 312.70 Disqualification of a clinical investigator.

(a) If FDA has information indicating that an investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50, or Part 56, or has submitted to the sponsor false information in any required report, the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research will furnish the investigator written notice of the matter complained of and offer the investigator an opportunity to explain the matter in writing, or, at the option of the investigator, in an informal conference. If an explanation is offered but not accepted by the Center for Drug Evaluation and Research or the Center for Biologics Evaluation and Research, the investigator will be given an opportunity for a regulatory hearing under Part 16 on the question of whether the investigator is entitled to receive investigational new drugs.

(b) After evaluating all available information, including any explanation presented by the investigator, if the Commissioner determines that the investigator has repeatedly or deliberately failed to comply with the requirements of this part, Part 50, or Part 56, or has deliberately or repeatedly submitted false information to the sponsor in any required report, the Commissioner will notify the investigator and the sponsor of any investigation in which the investigator has been named as a participant that the investigator is not entitled to receive investigational drugs. The notification will provide a statement of basis for such determination.

(c) Each IND and each approved application submitted under Part 314 containing data reported by an investigator who has been determined to be ineligible to receive investigational drugs will be examined to determine whether the investigator has submitted unreliable data that are essential to the continuation of the investigation or essential to the approval of any marketing application.

(d) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the data remaining are inadequate to support a conclusion that it is reasonably safe to continue the investigation, the Commissioner will notify the sponsor

who shall have an opportunity for a regulatory hearing under Part 16. If a danger to the public health exists, however, the Commissioner shall terminate the IND immediately and notify the sponsor of the determination. In such case, the sponsor shall have the opportunity for a regulatory hearing before FDA under Part 16 on the question of whether the IND should be reinstated.

(e) If the Commissioner determines, after the unreliable data submitted by the investigator are eliminated from consideration, that the continued approval of the drug product for which the data were submitted cannot be justified, the Commissioner will proceed to withdraw approval of the drug product in accordance with the applicable provisions of the act.

(f) An investigator who has been determined to be ineligible to receive investigational drugs may be reinstated as eligible when the Commissioner determines that the investigator has presented adequate assurances that the investigator will employ investigational drugs solely in compliance with the provisions of this part and of Parts 50 and 56.

(Collection of information requirements approved by the Office of Management and Budget under control number 0910–0014)

[52 FR 8831, Mar. 19, 1987, as amended at 52 FR 23031, June 17, 1987; 55 FR 11580, Mar. 29, 1990]

6. APPENDICES

APPENDIX A — BIOPSY KIT DIRECTIONS FOR USE

APPENDIX B — CLINICAL STUDY NO. 002: CLINICAL STUDY MATERIAL ACCOUNTABILITY LOG

APPENDIX C — CLINICAL PROTOCOL NO. 002: CLINICAL STUDY MATERIAL DELIVERY, RECEIVING, AND DISPOSITION OF SYRINGE RECORD

APPENDIX D — PROCEDURE FOR RESUSPENDING CELLS

CLINICAL PROTOCOL 002: PROCEDURE FOR RESUSPENDING CELLS

The following series of steps should be completed just prior to implantation. The process will take approximately 15 minutes. This time will allow for full resuspension of the cells.

1. If you have not already done so, unpack the transport box and remove the inner styrofoam box containing the syringe for injection. Retain all packing materials. Verify that the Patient ID number on the syringe and pouch matches that of the patient to be implanted.
2. Each syringe is individually packaged within a clear sealed pouch. Hold the pouch up to the light and observe the contents. The syringe will be capped with a black stopper on the tip, and will have a flexible plastic collar around the plunger to prevent the plunger from moving. **DO NOT REMOVE THE SYRINGE FROM THE POUCH, AND DO NOT REMOVE THE BLACK STOPPER OR THE PLASTIC COLLAR.**
    - During transport, the cells should have settled into a pellet against the barrel and/or plunger of the syringe. If you note any unusual observations (*e.g.* moisture in the pouch, cracks in the syringe barrel, missing collar, warm to the touch, etc.), contact Clinical and Regulatory Affairs, at .
3. Leaving the syringe in the pouch, flick the barrel of the syringe in the area where the cells have settled, until the cells completely detach from the syringe wall. Be careful not to flick your finger too close to the black stopper. Now invert the syringe 10 times.
4. Place the pouch containing the syringe on the nutator rotating platform on its long axis using one or two rubber bands to hold the pouch in place (keep the rubber bands away form the plastic collar on the plunger).
5. Allow the platform to rock for 10 minutes.
6. Turn off the nutator and remove the pouch containing the syringe. Hold the pouch up to the light and observe the contents of the syringe. When the cells are completely and uniformly resuspended, the contents of syringe will have an opalescent appearance with no obvious cell clumps.
7. If you observe clumps, flick the barrel and invert the syringe several more times until the appearance of the contents of the syringe is uniform.
8. If necessary, repeat steps 3-7 until the desired uniform consistency is obtained. **DO NOT PROCEED BEYOND THIS STEP UNTIL ALL VISIBLE CLUMPS ARE DISPERSED.**
9. Remove the syringe from the pouch. The flexible plastic collar around the syringe plunger is slit along its long axis. Open the collar at this lengthwise slit and carefully remove the collar from the syringe plunger. The syringe is now ready for implantation.